Digitized by the Internet Archive
in 2018 with funding from
University of Toronto

https://archive.org/details/medjournalDec1948uoft

THE UNIVERSITY OF TORONTO
MEDICAL JOURNAL

VOLUME XXVI TORONTO, DECEMBER, 1948 NUMBER 3

BRIGHT'S DISEASE[1]

ARTHUR E. PARKS, M.D., M.R.C.P. (London)[2]

The purpose of this paper is to present a review of the subject of Bright's Disease for students. It is not pretended that this presentation will be exhaustive in detail, but rather that it will serve as a guide in their studies of an admittedly difficult subject.

The term "Bright's Disease" is intended to cover a group of degenerative, inflammatory, and vascular diseases of the kidneys for which no definite causes have been found. The classification used in this article is that used commonly in clinical teaching.

DEGENERATIVE BRIGHT'S DISEASE

Chronic Lipoid Nephrosis

INFLAMMATORY BRIGHT'S DISEASE

A. Acute Diffuse Glomerulonephritis
B. Subacute Diffuse Glomerulonephritis
C. Subchronic Diffuse Glomerulonephritis
D. Chronic Diffuse Glomerulonephritis

VASCULAR BRIGHT'S DISEASE

A. Essential Hypertension
B. Malignant Hypertension

CHRONIC PYELONEPHRITIS

It is necessary, at the outset, to remember that the kidneys are a pair of highly vascular organs whose function it is to rid the blood stream of the waste products of metabolism brought to them by way of the renal arteries. This function is performed by the action of thousands of microscopic units called nephrons. Each nephron is composed of a filtering head called a glomerulus and a system of tubules which conveys the glomerular filtrate to the renal pelves. In the course of its journey, the glomerular filtrate becomes concentrated by the reabsorption of water, salt, and other crystalloids. It is considered that, under resting conditions, a limited number of nephrons are functioning; as the work of the kidneys increases, the number of functioning nephrons likewise increases, until the majority or all are engaged in clearing the blood of waste products. Nature has endowed man with a great renal reserve—so much so that it is possible to lose three-fourths of the total renal functioning tissue without the supervention of renal failure.

[1]Reprinted with minor modifications, by popular request, from THIS JOURNAL **20**, 117-139 (Jan.-Feb. 1943).

[2]Formerly of the Department of Medicine, Toronto Western Hospital.

CLINICAL PHENOMENA

It will be clear to anyone who studies the subject of Bright's Disease that there are five clinical phenomena that require some understanding before we proceed to a discussion of the various forms.

A. Albuminuria

It is generally considered that albumin found in the urine is the same as that found in the blood, and that the phenomenon reflects a state of increased permeability of the capillary tufts of the glomeruli. Recent investigations by Addis, however, have cast some doubt on the above hypothesis. It has been shown that the glomerular filtrate may contain albumin normally, and that such albumin is normally reabsorbed by the tubules. The explanation of the finding of albumin in the urine might then be defective tubular reabsorption, increased glomerular permeability, or a combination of both. In heart failure it is possible that increased hydrostatic pressure in the glomeruli may be an alternative or added factor.

B. Edema

This condition may be defined as the occurrence of an increased quantity of fluid within the peripheral intercellular spaces. A puffy appearance is imparted to the part, and the pressure of an examining finger leaves a pit or depression that is slow in disappearing. There are eight well-known types of edema, but only three will be mentioned here because they alone have a bearing on the subject of Bright's Disease.

1. Nephritic Edema

This type is characteristically found in the non-dependent parts of the body, especially in the loose peri-ocular, areolar tissues. It is considered to be a manifestation of widespread, increased capillary permeability. The edema fluid contains no globulin but about 1% albumin.

2. Nephrotic Edema

This variety of edema is also widespread in distribution and is not confined to the dependent parts of the body. It is due to a pre-renal deviation of the water and salt produced by a marked reduction in the osmotic pressure of the blood as a result of depletion of the blood albumin by prolonged albuminuria. It is not believed that the capillaries are abnormally permeable anywhere in the body but in the glomerular tufts. The principles of the Donnan equilibrium govern the transudation of water and salt from the blood to the tissue spaces. The concentration of albumin in this edema fluid is, therefore, low—less than 0.1%.

3. Cardiac Edema

This type of edema is characteristically dependent in distribution and, as Starling has shown, is due to the increased hydrostatic pressure of the blood in the terminal capillaries as a result of myocardial weakness. There may be also some degree of increased capillary permeability as a result of disturbed nutrition of the parts. The albumin content is about 0.7%, that is, intermediate between that of nephritic and nephrotic edema.

C. Azotemia, or Renal Insufficiency

The excretion of nitrogenous products, such as urea and creatinine, is, perhaps, the most important function of the kidneys. This constant regulating mechanism is reflected in health by a non-protein nitrogen content of the blood that lies between 25 and 35 mg. per 100 cc. It is believed that these nitrogenous materials pass through the glomerular tuft by a process of filtration. In the absence of glomerular filtration, nitrogen excretion fails to occur and the non-

protein nitrogen content of the blood begins to rise above its normal figure. As mentioned above, such does not occur until more than three-quarters of the functioning nephrons are destroyed. The occurrence then, of nitrogen retention may be evidence of severe renal damage, either transient or permanent. The retention of nitrogenous products, urea and creatinine, will not of themselves produce true uremia. Nitrogen retention, however, is always present in high degree when true uremia exists, that is, nitrogen retention is always a part of the clinical picture of true uremia. Renal disease is only one of several causes of nitrogen retention but it is probably the commonest. True uremia is a fatal toxemia due to failure of renal function, with non-protein nitrogen levels that may reach 300 mg. per 100 c.c. Usually, some degree of hypertension co-exists, but not necessarily so; the blood pressure may be quite normal. These patients exhibit a slowly progressive apathy leading to a state of mental stupor and coma. Muscular twitchings occur but epileptiform convulsions are seldom seen. The twitchings are probably due to tetany produced by the low serum calcium in this condition. An increasing acidosis is evidenced by a declining CO_2 combining power of the blood and the development of Kussmaul breathing. Death occurs in a state of deep coma.

D. Hypertension

Hypertension is said to exist whenever the blood pressure exceeds 140/92/90, the last figure being the diastolic fifth point taken at the total disappearance of all sound. In general, it is believed that a high diastolic pressure is more important than a high systolic. Because hypertension is present in all forms of Bright's Disease except nephrosis and early subchronic nephritis, it is very important to have some understanding of its production.

There is a type of individual known as a vascular hyperreactor who reacts abnormally to nervous stimuli. A sudden shock, such as immersing the hand for a few seconds in ice water causes an abnormal rise in the blood pressure and in the pulse rate. These individuals are jumpy and high-strung, and probably form the pool from which cases of Essential Hypertension are recruited. It would thus appear that a neurogenic basis underlies early high blood pressure.

On the other hand, the results of many investigations of the last decade have proved beyond all doubt that a humoral mechanism, by means of a vaso-pressor substance, is a cause of experimental hypertension in animals. The similarity of the lesions so produced to those found *post mortem* in man suggests strongly that some such humoral mechanism exists in many forms of human hypertension. It appears that partial renal ischemia causes the elaboration of a substance called renin within that kidney. In animals, this partial ischemia may be produced by a silver clamp placed on the renal artery. Although not proven, it appears that in man a state of functional hypertonus of the afferent arterioles to the glomeruli may cause a similar production of renin by a state of partial ischemia, and resultant decreased renal blood flow. The substance renin, being washed out of the kidney by the venous blood, unites with a substance normally present in the blood-stream called renin-activator or pre-angiotonin. The result is the production of a true pressor substance called angiotonin, or hypertensin. Exactly how angiotonin produces hypertension is not known; presumably, it does so by exerting a spastic effect on the splanchnic arterioles, thereby raising the peripheral resistance.

The effect of the increased peripheral resistance is to raise the diastolic blood pressure which, in turn, increases the work of the left ventricle of the heart, which is reflected by a rise in the systolic blood pressure. It appears from recent work of Wilson and Byrom that a vicious circle is thereby established and that the raised pressure causes further obliterative changes to occur in the vulnerable arterioles of the kidney. The result of this process is probably the further production of renin and a resulting increase in hypertension and damage to the cardio-vascular system. It will be clear, then, that any chronic disease that diminishes progressively the blood supply to the kidney can set up a vicious circle that leads eventually to sustained hypertension. Thus it is that essential hypertension, chronic diffuse glomerulonephritis, chronic pyelonephritis, hypertensive renal disease following toxemia of pregnancy, and the chronic hypertension of lead workers, may all produce hypertensive disease states which in the end stages may be so similar that only the history would serve to differentiate them. It is important, therefore, to realize that, while we must have some form of working classification of Bright's Disease, the divisions and subdivisions are by no means always clearcut. Indeed, more often than not, the patient presents a very mixed picture.

E. Hypertensive Encephalopathy

Irrespective of the cause of the hypertension, there emerges, in certain cases of Bright's Disease, a clinical syndrome characterized by convulsive epileptiform seizures which are due entirely to the hypertensive state. This clinical syndrome used to be confused with true uremia, but is now easily recognized by the characteristic convulsions, the elevated blood pressure, and the normal, or but moderately elevated, non-protein nitrogen in the blood.

It is believed that in these cases, hypertension is associated with an abnormal tendency to cerebral arteriolar spasm. This condition produces a state of cerebral ischemia, with or without cerebral edema. The result is a convulsive seizure with very high blood and cerebro-spinal fluid pressures. It can be treated very successfully be venesection, lumbar puncture, and dehydrating measures such as the intravenous administration of 50% glucose or sucrose. These measures, however, afford but temporary relief and the patient usually dies of a massive cerebral hemorrhage or cardiac failure.

With these clinical phenomena in mind, we may now proceed to a discussion of the various forms of Bright's Disease. Although widespread pathological changes occur, with few exceptions, only those changes found in the kidneys will be described.

DEGENERATIVE BRIGHT'S DISEASE

Chronic Lipoid Nephrosis

Chronic lipoid nephrosis or pure nephrosis is the only disease that will be considered under this title. It is true that poisoning by heavy metals and amyloid disease will cause degenerative changes in the kidney, but these conditions are not usually considered examples of Bright's Disease.

Definition: Nephrosis has been well defined by Bennett as a name applied to a group of rare cases exhibiting albuminuria and a tendency to edema, but without any history of hematuria or other evidence of acute nephritis, and without any signs such as hypertension, cardiac hypertrophy, and retinitis to indicate involvement of the cardio-vascular system.

Etiology: The cause of the disease is unknown. Some observers deny the existence of the disease; some believe it to be a form of mild nephritis. It occurs almost exclusively in children and young adults.

Pathology: Macroscopic: The kidney is of the "large white" variety, being considerably enlarged, soft, and edematous. The capsule is readily stripped from the smooth, pale, glistening surface which is thickly encrusted with opaque creamy-yellow flecks.

On section, the cortex is wide and sharply demarcated from the darker medulla. The pattern is straight but slightly blurred. In some cases, it is of a uniform creamy-yellow colour; in others, it presents a variegated appearance with alternating sections of opaque creamy masses and pale translucent renal tissue. Long radiating yellowish streaks descend into the pyramids of the medulla.

Microscopic: There is an absence of proliferative changes in the glomeruli, and a complete absence or very slight amount of any inflammatory infiltration.

The conspicuous feature is a widespread lipoid infiltration of the tubular epithelium. Anisotropic fat droplets are deposited extensively in the proximal convoluted tubules and the ascending limbs of the loops of Henle. The nuclei of these cells are degenerated and there are many hyaline and granular casts in the lumina.

The interstitial tissue, particularly the periglomerular and adventitial, is edematous. Interstitial infiltration is usually absent, but if present is extremely slight in amount and of low grade, consisting almost exclusively of lymphocytes and plasma cells.

Pathological Chemistry: The most important chemical change in nephrosis is a very great diminution in the plasma proteins. This diminution is at the expense more of the albumin than of the globulin fraction. The albumin content of the plasma falls from 5 to less than 2 grams per 100 cc. while the globulin remains at about 2—2.5 grams. It is the fall in the osmotic pressure of the blood consequent on the loss of albumin that is the cause of the pre-renal deviation of water and salt and the resulting nephrotic edema.

The cholesterol content of the blood is increased in nephrosis well above the normal level of 170 mg. per 100 cc.; often the level approaches 500 mg. per 100 cc., and levels as high as 1000 mg. per 100 cc. have been recorded. There appears to be little doubt that the cholesterol ester found in the kidney is deposited there from the over-charged blood and that the tubular change is not a degeneration but a true infiltration. This cholesterol ester is cholesterol oleate or palmitate. In association with the hypercholesterolemia and renal desposition of esters, various amounts appear in the urine and can be detected by the heat test under polarised light. Normally, 1.7—4.2 mg. are excreted daily; in nephrosis, as much as 16—42 mg. are excreted daily. It seems probable that the glomeruli are abnormally permeable, not only to albumin but also to cholesterol ester.

No complete explanation has been found for the hypercholesterolemia of nephrosis. It seems likely that it is associated in some way with the deficit of serum albumin, possibly a reflection of a state of malnutrition. The fat content of the diet bears no relation to the level of the blood cholesterol, although raising the intake of ingested fat does tend to increase the level of neutral blood fat—a lipemia that also may occur in nephrosis. Despite the great elevation of the blood cholesterol, edema fluid and transudates, though frequently opalescent, have a low cholesterol content (1.5—0.5 mg

per 100 cc.). This finding, together with the presence of a low protein content, suggests that abnormal capillary permeability plays no part in the production of nephrotic edema.

The blood calcium in nephrosis is somewhat reduced, while tests of renal function give figures very little, if at all, below those of normal health. Nitrogen retention does not occur and there is no inability to excrete salt or water. The oliguria that occurs is due to the prerenal deviation of salt and water to the tissues.

Clinical Picture: Nephrosis occurs usually in a child or young adult. Often it is discovered in its early stages by a routine medical examination when heavy, constant albuminuria is found unaccompanied by the presence of red blood cells or granular casts. The individual otherwise feels and looks completely well with no edema or hypertension and with perfectly normal renal-function tests. The examination of the heart and ocular fundi reveals no abnormality. Sooner or later, however, weakness and the appearance of edema attract attention. The edema is observed first in the dependent parts, but later is seen in the thighs, scrotum abdominal wall, thoracic wall, back and face. Ascites, and later hydrothorax, often develop. The basal metabolism is low—about -20%. Anemia is usually absent, although occasionally present in marked degree and of secondary type with low colour index.

The subsequent course of nephrosis is that of persistent stubborn massive edema associated with heavy albuminuria and oliguria. The disease continues for months or years with fluctuating periods of remission and relapse. Often the patient's hopes are raised by diuresis and the temporary decrease or disapearance of edema. Only too often they are dashed to the ground by the sudden reappearance of massive dropsy. The disease is particularly trying, for the patient feels otherwise in good health. Occasionally, the edema disappears while the albuminuria persists, and, rarely, both edema and albuminuria disappear when the patient makes a spontaneous recovery. It would appear that, when recovery occurs, the leak of albumin through the glomerular tufts ceases, allowing a replenishment of the serum protein and a restoration of the colloid osmotic pressure of the blood. Possibly there is an improved re-absorption of albumin by the tubules. More often, however, secondary infections, such as pneumococcal peritonitis, bronchopneumonia, or streptococcal septicemia, cause a fatal termination.

Differential Diagnosis: Chronic lipoid nephrosis must be differentiated from subchronic nephritis. The distinction is made only by prolonged study and observation. A history of an antecedent attack of acute glomerulonephritis makes one favour subchronic glomerulonephritis, but this diagnosis is established by the appearance of hematuria, hypertension, changes in the fundi, and a rising blood non-protein nitrogen. Such changes never occur in pure nephrosis.

Treatment: The most important items in the treatment of nephrosis are prolonged rest in bed, a diet with about 70 or 80 grams of protein per day, and the maintenance of morale by the provision of a bright environment and an attitude of cheerful confidence in the outcome.

In accord with Epstein's teaching, a diet with a liberal quantity of protein is provided in order to replace the albumin lost in the urine. It has been found that a diet containing 100 grams or more of protein per day is impracticable, because the average nephrotic patient will not eat it. It is essential to restrict all salt in the diet and reduce the daily fluid intake

to 1200 — 1500 cc. Thyroid extract may be given and is occasionally dramatically successful. Peculiarly enough, however, even large doses more often have little effect. If anemia be present, it is wise to administer iron as 5 grains of ferrous sulphate three times daily with meals. Because hematuria and nitrogen retention are absent, it is permissable to try the effect of intravenous Mersalyl, preferrably after the administration of 90 grains of ammonium chloride. If no significant diuresis results, it should not be repeated. It is very essential to remove all foci of infection in the body—notably diseased tonsils and teeth. Large collections of fluid in the serous cavities, hydrothorax and ascites, are removed by mechanical drainage when they fail to disappear by diuretic measures. Decapsulation of the kidneys has found no convincing support. Pneumococcal secondary infections should be treated by an appropriate course of a sulphonamide, paying particular attention to possible urinary complications, or an antibiotic.

INFLAMMATORY BRIGHT'S DISEASE

A. Acute Diffuse Glomerulo-Nephritis

Synonyms: Acute diffuse nephritis, Acute toxic nephritis, First stage glomerulonephritis.

Definition: Acute diffuse glomerulonephritis is an acute inflammation of the glomeruli of the kidneys, which is associated with evidence of widespread capillary damage throughout the body.

Etiology: The exact mechanism by which acute glomerulonephritis arises is unknown. The disease almost always follows an acute upper respiratory infection, or some other acute infection such as scarlet fever or erysipelas. Infections due to the haemolytic streptococcus have been regarded with more suspicion than those caused by other micro-organisms. A great deal of investigation has been carried out in an effort to elucidate the etiology of acute glomerulonephritis because it is believed generally that other forms of Bright's Disease are causally related to an antecedent attack of acute glomerulonephritis. It is significant that the attack characteristically occurs, not during an acute infection, but about ten to fourteen days after that infection has subsided. Furthermore, it is usual for an acute nephritic to excrete a sterile urine; cultures from the kidneys of a patient, *post mortem*, are sterile. The blood of an acute nephritic fails to yield living organisms. For these and other reasons, it is believed that acute glomerulonephritis is not an acute infection in the kidneys but an unusual form of allergic response characterized by spasm and later leakage of capillaries throughout the body. The capillaries of the glomerular tufts of the kidneys appear to be the most vulnerable and the most damaged of the body. Certainly, the whole course of the disease is dominated by the progress of the renal lesions. In the majority of cases, the process is reversible and complete recovery occurs; it is believed, however, that chronic glomerulonephritis is always antedated by an attack of acute glomerulonephritis, possibly so mild that it is not remembered by the patient. Campbell has called attention to the wisdom of making a routine of examining the urine within a few days of recovery from all acute respiratory infections. It is probable that this measure will reveal instances of mild, acute glomerulonephritis which would otherwise be overlooked, and which might, if neglected, later contribute to the number of "idiopathic" chronic nephritides. Exposure to cold and wet

is an important predisposing factor in the development of the disease.

Pathology: Macroscopic: Both kidneys are involved and are usually slightly enlarged, grayish or reddish in colour, soft in consistency, and studded with tiny red hemorrhagic dots. The capsule strips readily.

On section, the cortex is well demarcated from the medulla which is of a congested purplish-brown colour. Hemorrhagic glomeruli are noted as red dots throughout the cortex.

Microscopic: Attention is focussed on the glomeruli which are almost all involved from the earliest stages. The typical glomerulus is enlarged, highly cellular, and often almost bloodless due to swelling and proliferation of the capillary endothelium. The partial or complete occlusion of the capillary lumina by this process severely impedes, and occasionally completely obstructs, the circulation of blood in the glomerulus. This highly cellular, swollen condition of the glomerulus is described by Russell as "proliferative glomerulitis". In addition to these proliferative changes in the cells of the tufts, the glomeruli are invaded by numbers of neutrophilic leucocytes which occupy the capillary lumina and often the stroma of the tuft. Hyaline thrombi are sometimes present in the capillaries of the tufts, and occasionally erythrocytes and neutrophilic leucocytes are observed in the capsular spaces.

The tubular epithelium of the kidneys shows widespread albuminous (cloudy swelling) and hydropic degeneration. In addition, when the inflammatory changes in the glomeruli are intense, hyaline degeneration of the tubular epithelium is obvious, whereas, when the changes are mild, fatty and especially lipoid degeneration occurs.

The lumina of the tubules contain large numbers of erythrocytes and a variable number of neutrophilic leucocytes. Granular and hyaline casts are commonly seen in the loops of Henle and in the collecting tubules.

The interstitial tissue is frequently edematous, but there is no fibrosis or any evidence of proliferation of fibroblasts. There is remarkably constant infiltration of the periglomerular tissues with neutrophilic leucocytes; the same infiltration is observed in the periadventitial tissues of the vasa afferentia.

The other blood vessels of the kidneys show no gross abnormalities. Hemorrhage occurs occasionally into the tubules and less frequently into the interstitial tissues.

The pathological changes in the body, other than the kidneys, have received scant attention. Ellis has stressed the fact that the heart is embarrassed in certain cases of acute glomerulonephritis, particularly in children. A certain degree of cardiac enlargement occurs, but there are no detailed accounts of changes in the coronary arteries in fatal cases.

The edema of acute nephritis is usually widespread, and is due to damage and increased permeability in the parts affected.

Pathological Chemistry: There is a slight to moderate degree of impairment of renal function in cases of acute glomerulonephritis that do well. It is common to observe transient nitrogen retention with N.P.N. levels of 50 to 60 mg. per 100 cc. of blood. Severe, fatal cases of acute glomerulonephritis die a uremic death with very severe impairment of renal function and N.P.N. levels of 100 mg. or more per 100 cc. of blood.

Clinical Picture: Typically, acute glomerulonephritis occurs in children and young adults. The onset is usually fairly sudden—about ten to fourteen

days after an acute upper-respiratory infection. Attention is attracted to the patient by the development of edema around the eyes and the frequent passage of scant, dark, smoky or bloody urine. The edema spreads to involve the whole face and usually the trunk and lower extremities. Often the patient complains of headache, pain in the back over the kidneys, anorexia, nausea, and sometimes vomiting. The temperature is usually elevated slightly to 99 or 100°F.; occasionally, high fever and chills occur. The pale, pasty, puffy appearance of the patient suggests an anemic condition. The examination of the blood, however, reveals a normal hemoglobin and red-blood count. The white-blood count is normal or somewhat elevated. Examination of the heart in children occasionally reveals slight but definite enlargement. This enlargement is accompanied by moderate hypertension and a variable degree of dyspnea. More often, the heart is normal in size and there are no subjective symptoms of cardiac insufficiency. A moderate transient elevation of the blood pressure is, however, a fairly constant finding.

The urine characteristically is passed frequently and is small in amount. It contains gross and microscopic blood in large quantities, much albumin, numerous pus cells, and large numbers of granular and red cell casts. The specific gravity of the urine is high—from 1.022 to 1.032.

The average case of acute glomerulonephritis progresses favourably and ends in complete cure. In the course of three or four days, the edema subsides, the urine becomes more abundant and lighter in colour, and such symptoms as headache, restlessness, sleeplessness, nausea, and vomiting disappear. The urine begins to clear as shown by decreasing albuminuria, hematuria, pyuria, and cylindruria. The casts disappear first and the blood and albumin last. Soon the patient is symptom-free, and, before long, has a normal urine and is considered cured. The average duration of an attack of acute nephritis is about six weeks.

Not all cases, however, follow the above course. The disease may be prolonged over several months before a cure results. During this time there are fluctuating degrees of edema, hematuria, and albuminuria. Eventually, however, the symptoms and signs of the disease disappear.

A few cases follow a fulminating, downhill course with massive albuminuria, hematuria, moderate edema, and the development of sustained hypertension and renal insufficiency. The ability to concentrate the urine fails and the patient dies in a state of true uremia, of hypertensive encephalopathy, or of cardiac failure.

Prognosis: Nearly all cases that can be recognized clinically recover. A few follow the atypical courses outlined above. Probably many cases are never recognized by either patient or doctor and are the cause of many insidious forms of inflammatory Bright's Disease seen in later life.

Differential Diagnosis: Acute focal nephritis may occur during the course of many acute infections. It is recognized and differentiated from acute diffuse glomerulonephritis by hematuria without casts, by the absence of edema, hypertension and nitrogen retention, and by the fact that the disease occurs during an infection rather than ten to fourteen days after it. Subacute bacterial endocarditis causes its own form of focal nephritis and hematuria. It is recognized by finding the other usual signs of that disease.

Treatment: The essential of treatment is rest for the kidneys. This rest is accomplished by putting the patient to

bed and by giving a diet that imposes the least work on the kidney compatible with the proper nutrition of the patient. It is usual to give him a diet of 800 cc. of milk daily or 1000 cc. of fruit juice (orange juice, grapefruit juice, etc.). The patient is kept strictly in bed and given full nursing care. He is kept on the above diet until the edema is gone and the urine free of blood and albumin. Usually a period of one to two weeks is necessary to accomplish this result. At the end of this time the patient is allowed one portion of carbohydrate with each meal in addition to the usual milk. At the end of a week, if there is no return of albumin, he is allowed two portions of carbohydrate with each meal. At the end of another week, if still no albuminuria exists, he may be given a diet of CHO = 250, P = 40, F = 80, and fluids up to 1200 or 1500 cc. daily. If a trace of albumin appears and lasts three days, the diet must be reduced to the previous lower level. If, at the end of a week on a high carbohydrate diet, there is no urinary abnormality, the patient may start to sit up, and at the end of another week he may be allowed to walk. If the urine remains clear for two weeks, the protein may be raised to 60 grams, and subsequently to 80 grams per day. Thereafter, the patient should never eat more than 80 grams of protein daily. A return of albuminuria and hematuria indicates a return to bed rest and restricted diet. Only after the patient has been up and around and free of all signs of disease for three weeks should one consider removal of foci of infection.

Occasionally one encounters acute glomerulonephritis with persistent slight hematuria and albuminuria, despite the strictest dietetic and nursing care. These cases should be kept in bed for one month after all signs of improvement have ceased when they may be allowed up, for it is practically impossible to keep them in bed any longer.

It is important to emphasize the need for patience and prolonged rest to secure complete disappearance of all urinary abnormalities. A complete cure is possible only in the acute stage of glomerulonephritis. Once the disease becomes chronic, cure is no longer possible.

Diuretics have no place in the treatment of acute glomerulonephritis, and there is no medicine that has a beneficial effect on the course of the disease. Sweating and other forms of physiotherapy are no longer employed. Surgical decapsulation of the kidney has not received the approval of the profession. It is important to warn the patient against subsequent exposure to cold and wet.

B. Subacute Diffuse Glomerulonephritis

Synonym: Subacute diffuse nephritis.

Definition: A disease which is really a serious progressive form of acute glomerulonephritis, characterized by remissions and exacerbations, and usually terminating in the uremic death of the patient.

Etiology: The cause of this disease is the same as that of acute glomerulonephritis.

Pathology: Macroscopic: The kidneys are enlarged and edematous, and the colour varies from a grayish-red or pink to a deep mahogany red, according to the degree of congestion. Petechial haemorrhages are scattered over the sub-capsular and cut surfaces, and specks of lipoid are frequently present.

On section, the cortex is deep, the pattern blurred, and the demarcation from the medulla indistinct. The glomeruli appear to the naked eye as glistening gray dots. The medulla is marked by poorly-defined opaque white streaks.

Microscopic: The characteristic change noted in these kidneys is in the glomeruli where Bowman's capsule undergoes such marked proliferation that so-called epithelial crescents or demilunes are formed. This change is described as "proliferative capsulitis" by Russell and is the hallmark of very severe inflammatory damage to the glomeruli. This finding is constantly present, but is unevenly distributed throughout the cortex; some glomeruli are markedly affected while others are but little changed or may escape entirely. Proliferative glomerulitis is also constant and affects all the tufts. It is common to observe adhesions between the tufts and the epithelial crescents growing up from the hyperplastic Bowman's capsules. These adhesive bridges are soon invaded by spindle fibroblasts with a resulting complete destruction by fibrosis of a large number of glomerular tufts. Leucocytic infiltration of the tufts and demilunes is always present and is also often noted in the capsular spaces. Hyaline degeneration of the epithelial cells of Bowman's capsule is frequently present.

The characteristic changes which occur in the tubules are albuminous (cloudy swelling), hydropic, hyaline and lipoid degenerations of the epithelium. Hyaline degeneration predominates over lipoid degeneration, although both coexist. The tubular lumina contain numerous erythrocytes, leucocytes, desquamated epithelial cells, and all forms of casts—granular, leucocytic, erythrocytic, lipoid and hyaline.

Edema and diffuse fibrosis are the changes that occur in the renal interstitial tissue. The fibrosis involves the cortex and outer medulla and is most marked around the glomeruli. The interstitial tissue is infiltrated diffusely with very numerous neutrophilic and eosinophilic leucocytes, plasma cells, and small lymphocytes. Small hemorrhages sometimes occur and lipoid is occasionally seen in the interstitial spindle cells.

The interlobular arteries and vasa afferentia sometimes show acute necrosis with purulent infiltration of the vessel walls. Slight medial hypertrophy is sometimes observed.

It would appear that these cases with marked proliferative capsulitis of the glomeruli correspond to the "extra-capillary" glomerulonephritis of Fahr. Cases of Bright's Disease with marked proliferative glomerulitis and little or no proliferative capsulitis correspond to Fahr's "intra-capillary" glomerulonephritis. In general, the former represents a severe inflammation resulting in a stormy course and rapid death from uremia; the latter indicates a milder course with recovery or a protracted low-grade chronic illness.

Pathological Chemistry: These patients develop renal insufficiency at various times, in variable degree, and finally, severely as a terminal result.

Clinical Picture: Subacute glomerulonephritis is the name given to those cases in which the urinary abnormalities, hypertension, edema, impairment of renal function and other manifestations of the acute stage do not abate, and, in fact, are intensified so that death from uremia results in a few months or, at most, two to three years. Most of the cases occur in the late thirties. These hapless victims follow a course of prolonged bed care with alternating periods of remission and relapse. Often when the physical and urinary signs are almost normal, a sudden flood of blood cells occurs in the urine with accompanying hypertension, morning headache and dyspnea. This deterioration in the patient's condition is often precipitated by the occurrence of an upper-respiratory infection, especially a sore throat. Sooner

or later, impairment of renal function becomes established with gradually mounting nitrogen retention. Death from uremia is the usual outcome, although some physicians claim to have observed a cure in a very few cases.

Differential Diagnosis: These cases are to be differentiated from those with acute glomerulonephritis. The distinction is made by the usual favourable course of the acute glomerulonephritic within a reasonably short duration of six weeks to two months. The difficulty lies in those cases of acute glomerulonephritis which take several months to heal. It may be impossible, in such cases, to tell just when acute glomerulonephritis ends and subacute begins. A story of repeated sore throats and resultant acute exacerbations of hematuria favours strongly a diagnosis of subacute glomerulonephritis.

Treatment: These patients are treated along the same lines as the acute glomerulonephritic. One must keep in mind constantly the nitrogen, water, and salt content of the diet. It may be necessary to steer a middle course between the dangers of uremia on the one hand and the presence of edema on the other. In this case, one regards nitrogen retention as a much more serious complication than edema. It is necessary, therefore, to allow the patient sufficient fluid to excrete his nitrogenous waste in a dilute urine. Despite the presence of hematuria, one is forced in these cases to advise removal of foci of infection in order to protect the patient from repeated exacerbations. This step is taken despite the danger of throwing the patient into uremia, because it is the only means of cure that is available. Sooner or later, however, nearly all the cases develop uremia and receive the usual treatment for that condition. An account of the treatment of uremia will be given under chronic glomerulonephritis.

C. Subchronic Glomerulonephritis

Synonyms: Chronic parenchymatous nephritis, Chronic hydremic nephritis, Chronic hydropigenous nephritis, Chronic nephritis with edema, Subacute nephritis of some authors, Second-stage glomerulonephritis.

Definition: A form of inflammatory Bright's disease characterized by prolonged, widespread, nephrotic edema, compensated renal function, and, in the early stages, by an absence of hypertension and cardiovascular hypertrophy.

Etiology: Commonly, no cause for the disease can be discovered. Occasionally, a history of acute glomerulonephritis many years before is obtainable. Not infrequently, an attack of scarlet fever, with or without hematuria, will be remembered. It is probable that most of these cases are the direct expression of a low-grade smouldering inflammation of the kidneys caused by the ordinary common cold or influenzal attack to which man is so frequently subject.

Pathology: Macroscopic: The kidneys are enlarged and edematous and are typically of the "large, white" variety. The capsule strips readily and exposes a smooth, or finely granular, straw-coloured, or grayish-white, surface studded with closely-packed lipoid flecks. Petechial haemorrhages are rarely present, and in their absence, this kidney, macroscopically, cannot be differentiated with certainty from the large, white kidney of chronic nephrosis.

The cortical pattern is blurred and is poorly demarcated from the medulla. Lipoid is seen as opaque yellow streaks in the medullary pyramids. In the later stages, the arteries in the intermediate zone are more prominent than in normal specimens.

Microscopic: The outstanding glomerular change in this group is the degree of proliferative glomerulitis. Proliferative capsulitis is also present, but is a less conspicuous feature. The degree of proliferative glomerulitis present is greater in these kidneys than in any other form of Bright's Disease. The rare glomerular tuft shows fibroblastic invasion and glomerular destruction. Apart from the proliferative glomerulitis, however, the glomeruli appear typically to be intact and there is very little evidence of progressive glomerular destruction. Lipoid degeneration of the capsular epithelium is present in most examples and hyaline degeneration is absent.

The tubular epithelium is conspicuous by the marked degree of lipoid degeneration and the absence of hyaline degeneration. Erythrocytes and neutrophilic leucocytes are less abundant in the lumina of the tubules, while desquamated epithelial cells and lipoid casts are more abundant.

The interstitial tissue is diffusely increased, although not so uniformly as in subacute glomerulonephritis. The fibrosis is characteristically periglomerular with accompanying regional tubular atrophy. Between these areas, the fibrosis is much less dense and encloses numbers of dilated tubules with flattened epithelial cells. The areas of atrophic tubules enclosed in fibrous tissue, alternating with those of dilated tubules in a loose stroma, are very striking. Conspicuous groups of foam cells ladened with lipoid are present in the interstitial tissues in all cases.

The arteries and arterioles of these kidneys show medial hypertrophy of variable degree.

Pathological Chemistry: The chemical pathology is the same as that of chronic nephrosis until renal insufficiency appears, when the finding of nitrogen retention is added to the characteristic lipoid and serum protein changes of nephrosis.

Clinical Picture: Subchronic glomerulonephritis occurs in both sexes and over a span of age from fifteen to sixty. Commonly, it is observed in the forties, though Russell found the average age of the group she studied to be twenty-six.

The illness begins insidiously with edema of the face and legs. These patients have been described well as those with pale, puffy faces and pale, white kidneys. It is common to observe this onset shortly after an acute upper-respiratory infection, and to find small numbers of erythrocytes in the urine. A state of progressive widespread edema associated with nausea, vomiting and abdominal pain may force the patient to his bed. More often, for a time, they continue their work in a state of chronic ill health. These are the nephritics with signs but few symptoms. The pale countenance may be a reflection of a true anemia, but is more often an expression of edema. At first, renal function is intact and tests of renal efficiency show good concentrating power of the kidneys and normal figures for the blood N.P.N. Later, however, these patients begin to suffer from nycturia with an obligatory polyuria. They are then in a state of compensated renal function and are able to eliminate the nitrogenous waste products by the excretion of an increasing volume of water. It is important to emphasize that, in these cases as in nephrosis, there is no inability of the kidneys to excrete the salt and water brought to them. The salt and water are pre-renally deviated to the tissues on account of the low-colloid osmotic pressure of the blood. As in nephrosis, this low colloid osmotic pressure is produced by the heavy albuminuria and resultant fall in the serum proteins. Towards the end of this stage

of nephritis, the destruction of renal tissue becomes so great that scarring and fibrosis appear to stop or decrease greatly the loss of albumin. This change is reflected by a rise in serum osmotic pressure and a disappearance of the nephrotic edema.

As the disease progresses from early to middle and late stages, evidence of cardiovascular damage appears. These patients begin to suffer from headaches and breathlessness on effort. Examination then reveals slight to moderately elevated blood pressure with figures around 160/94. The fundus oculi may reveal early arteriosclerotic changes in the vessels and a wet, edematous retina. A fair proportion pass into the stage of chronic nephritis, presently to be described, and die a uremic death. This outcome is especially apt to occur in the event of an acute exacerbation following an intercurrent upper-respiratory infection.

More often, a secondary infection, such as bronchopneumonia, causes the death of the patient. Edema of the lungs, due to cardiac failure, and acute peritonitis with ascites are other forms of termination of this disease.

It is important to stress the close clinical resemblance of this disease to chronic nephrosis. It is so close that in the early stages it may be impossible to tell them apart. There are those who believe that no such disease as chronic nephrosis exists and that such cases are, in fact, cases of subchronic nephritis with nephrotic edema.

Differential Diagnosis: Chronic nephrosis is differentiated from subchronic glomerulonephritis by the lack of any history of acute nephritis, and by the absence of hematuria at any stage. The distinction may be made only by the passage of time when such features as hematuria, hypertension, slight cardiac hypertrophy, early retinal changes, and impaired renal function point to the existence of subchronic nephritis. Should the patient die of an intercurrent infection before these changes occur, the only way to distinguish nephrosis from subchronic glomerulonephritis would be by the microscopic appearances of the kidneys described above, at *post mortem* examination.

Treatment: It is essential to protect the patient from acute exacerbations by removing all foci of infection, such as diseased tonsils and teeth, and by careful supervision of environmental conditions. The dietary management is the same as that of nephrosis, until nitrogen retention begins to appear. At that point it will be necessary to restrict protein in accordance with the method described for acute nephritis. Anemia is treated by iron therapy and the state of lowered metabolism by the administration of thyroid extract.

D. Chronic Diffuse Glomerulonephritis

Synonyms: Chronic interstitial nephritis, Chronic azotemic nephritis, Third-stage glomerulonephritis, Chronic toxic nephritis, Chronic nephritis without edema, Secondarily contracted kidney.

Definition: An end-stage form of chronic Bright's Disease, characterized by absence of edema and by the presence of nitrogen retention and, usually, also by cardiac hypertrophy and hypertension.

Etiology: It is believed that all of these cases arise from an antecedent attack of acute glomerulonephritis at some time in the past. Many of them have gone through the stage of subchronic glomerulonephritis to terminate in this form of the disease.

Pathology: Macroscopic: The kidneys are known as secondarily contracted kidneys. They are variable in size, firm to the touch, pale straw or gray in

colour, and possess a thickened capsule that is stripped with difficulty. The exposed surface is finely granular, due to a diffuse fibrotic scarring, with intervening islands of hypertrophied nephrons. A variable degree of contraction results in kidneys that may be normal in size or so small as to weigh together but 75 grams.

The cut surface presents a narrowed irregular cortex, so thin in places that the medullary pyramids almost reach the surface. The cortical markings are obliterated and demarcation from the medulla is blurred. Large portions of the cortex are replaced by a scattered meshwork of fibrosis. Yellowish streaks of lipoid are noted in the medullary pyramids, and marked thickening of the renal vessels is present in all cases where hypertension had been present for some time before death.

Microscopic: The glomeruli show a striking degree of proliferative glomerulitis which involves all the surviving glomeruli uniformly. Many of these glomeruli have reached the late stage of proliferative glomerulitis that is characterized by hyaline necrosis of the tufts. A variable degree of proliferative capsulitis is present. Adhesions between the tufts and Bowman's capsule are commonly found but are not conspicuous. Only a relatively small number of glomeruli disappear in consequence of complete destruction.

The tubular changes are those of atrophy and hypertrophy. Those tubules which drain the filtrate from badly damaged glomeruli undergo atrophy and a replacement fibrosis. The tubules of relatively undamaged intervening nephrons undergo hypertrophy. The tubular epithelium shows great albuminous, and occasionally hyaline, degeneration. The lumina contain neutrophilic leucocytes and variable numbers of erythrocytes, granular and hyaline casts.

Fibrosis of the interstitial tissue is diffuse throughout both kidneys. This increase in scar tissue is not entirely uniform, for there may be seen areas of denser fibrosis enclosing atrophied tubules and small islands of less dense fibrosis enclosing dilated tubules. A diffuse dense infiltration with inflammatory cells is present in the interstitium. It consists of lymphocytes, plasma cells, and a moderate number of neutrophilic leucocytes. A large amount of lipoid is contained within foam cells which lie in columns between the loops of Henle.

Cardiovascular hypertrophy may be slight, moderate or great, depending on the degree of pre-existent hypertension. Fatty, hyaline degeneration is constantly present in a few of the vasa afferentia, and a variable degree of ischemic glomerular atrophy may be seen.

Pathological Chemistry: The outstanding changes that occur in the blood are a rising blood urea and creatinine and a falling serum calcium—in other words, the changes of renal insufficiency and true uremia.

Clinical Picture: Chronic diffuse glomerulonephritis is most commonly encountered in young and middle-aged people before they have lived long enough to develop the arteriosclerotic changes of old age. There is no special sex incidence. Two main divisions of chronic glomerulonephritis are encountered; (*a*) those cases with a maximum degree of hypertension and a minimum of renal insufficiency, and (*b*) those with a minimum degree of hypertension and a maximum of renal insufficiency. Between these two extremes, the majority of cases of chronic glomerulonephritis present a mixed picture of both renal insufficiency and hypertension. A common history to obtain is that of antecedent protracted edema that has since disappeared and has been followed by a period of tiredness and chronic ill

health, leading to the condition presently to be described.

The patient of the predominantly hypertensive type consults the doctor because of tiredness, loss of weight, morning headaches, irritability, dizziness, visual disturbances, and shortness of breath on exertion. Occasionally, he may complain of attacks of nocturnal dyspnea and of swelling of the ankles. Commonly, he has been told he is pale and does not look well.

On examination, these patients are characteristically thin, dehydrated and free of edema. The ocular fundi show advanced hypertensive neuro-retinopathy with pale optic discs. The left ventricle of the heart is greatly enlarged and gallop rhythm may be present. The mitral first and aortic second sounds are accentuated. The peripheral arteries are thickened and tortuous. If left ventricular failure be present, there may be rales at the bases of the lungs or even greater degrees of pulmonary edema. Dependent cardiac edema is present in some cases. The blood pressure is extremely elevated, being as high as 234/120. These patients are prone to have attacks of hypertensive encephalopathy when they develop terrifying convulsive attacks with extremely high blood and cerebrospinal fluid pressures. The patient may die in one of these attacks which used to be called pseudo-uremia. A moderate degree of secondary anemia is usually present.

These cases all show a mild or moderate degree of renal failure with N.P.N. levels of 70—80 mg. per 100 cc. The urine has a low fixed specific gravity of about 1.012 and there is an obligatory polyuria and nycturia. The urine contains a small amount of albumin, numerous hyaline and waxy casts, and little or no blood unless there is an acute exacerbation. They are apt to die of cerebral haemorrhage, cardiac failure, or cardiac infarction.

The chronic nephritic of the uremic type presents a different picture. The story is one of progressive asthenia, anorexia, pallor and loss of weight. The patient is irritable and often drowsy and listless. He is very thirsty and complains of having to void large quantities of urine frequently both day and night. On examination, dehydration and rather marked anemia are found. The ocular fundi may show nothing but retinal arteriosclerosis. A slight or moderate degree of hypertension and cardio-vascular hypertrophy is found. Characteristically, one finds a very high N.P.N. of say 200 mg. per 100 cc., a creatinine level of 5 mg. and a blood calcium content of 9 mg. per 100 cc. The urine is of low specific gravity, 1.008 or 1.010, while the two-hour and other renal-function tests show great impairment of renal function.

These patients gradually become so weak that they are forced to bed and pass gradually into a state of true uremia. At this time, there may appear a pericardial friction rub which should always be searched for. They pass into a state of drowsiness, stupor, and finally coma, characterized by deep Kussmaul breathing with marked acidosis and a low CO_2 combining power of the blood. Muscular twitchings, but not convulsive fits, are characteristic and they finally die of respiratory failure in a state of profound uremic toxemia.

Differential Diagnosis: The hypertensive type of chronic diffuse glomerulonephritic must be distinguished from the patient in the end stage of essential hypertension. In the absence of a good previous history this distinction may be impossible. In general, however, the nephritic patient is pale and anemic while the hypertensive is not. The blood pressure in chronic glomerulonephritis is high, but, usually, not so

high as in terminal essential hypertension. The hypertensive chronic nephritic is usually younger than the essential hypertensive patient. Lastly, urinary abnormalities and moderate impairment of renal function are far more constant in hypertensive chronic glomerulonephritis than in essential hypertension.

The uremic type of chronic diffuse glomerulonephritic can scarcely be confused with anything but the so-called malignant hypertensive. The distinction here, too, may be impossible. The malignant hypertensive patient may likewise die of uremia, but the history is one of a much more fulminating illness, the degree of hypertension is much higher, and the ophthalmoscopic changes more marked. Cardiac damage is more extensive and anemia is less marked in the malignant hypertensive than in the uremic chronic nephritic.

Treatment: In brief, there is no satisfactory treatment of chronic glomerulonephritis. The best that can be done is to maintain the renal reserve as long as possible by a low-protein, high-carbohydrate diet and by allowing a sufficiency of fluid despite the possible development of cardiac edema. Restlessness and sleeplessness in the early stages may be controlled by the administration of barbiturates. Codeine may be given with aspirin for headache. Cardiac failure is treated by digitalizing the patient. The bowels should be kept free by the use of a saline laxative. Diuretics have no place in the treatment of chronic glomerulonephritis. The patient should be kept ambulatory as long as possible, but should be off his feet and resting for at least fourteen out of each twenty-four hours.

The treatment of hypertensive encephalopathy will be described below under the next title. Uremia is treated by absolute rest in bed and by the administration of a diet of fruit juices and fluid up to 2000 or 3000 cc. daily. If nausea and vomiting are present, one may administer 1500 or 2000 cc. of 5% glucose solution intravenously. The muscular twitchings and spasms can be stopped instantly by the slow intravenous administration of 5 cc. of 10% calcium chloride or calcium gluconate. Eventually, no treatment is of any avail and the patient succumbs.

VASCULAR BRIGHT'S DISEASE

A. Essential Hypertension

Synonyms: Hyperpiesa, Primarily contracted kidney.

Definition: A disease in which, in the early stages, the only detectable physical abnormality is an elevated blood pressure, and in which, in the later stages, cardiovascular hypertrophy and degeneration are predominant. Allbutt defined it as a condition of which a permanently-raised blood pressure is the dominating feature, associated with left-ventricular hypertrophy, terminaing usually in heart failure and sometimes in cerebral haemorrhage, and with little evidence of renal insufficiency.

Etiology: The cause of this disease is still unknown. In the beginning it is probably a manifestation of functional hypertonus of the splanchnic arterioles. It is possible that this functional hypertonus first manifests itself in the individual known as a vascular hyperreactor. This type of patient exhibits a blood pressure that it normal under conditions of ease and elevated under conditions of strain. Only when the blood pressure is consistently elevated is one justified in diagnosing essential hypertension. It seems probable that, after a certain point, the repeated hypertensive insults to the kidney result in a state of partial ischemia of the

afferent glomerular arterioles. Although not proven in man, it appears from the work of Wilson and Byrom that a vicious cycle is established by which the kidney undergoes progressive ischemic vascular damage. Under these conditions, hypertension is maintained and possibly made worse by the production of renin within the kidneys. It must be emphasized that this chain of events is entirely unproven, but appears likely in the light of recent work. We must not forget that all the changes that occur in hypertension may be the direct result of an initial transient hypertension, but just what causes this initial rise in blood pressure remains a mystery.

Pathology: Macroscopic: The kidney of essential hypertension has been described as the red granular, primarily-contracted kidney. Although this is the traditional description, it is a fact that, of Bell and Clawson's series of 420 cases, only 15% had "contracted kidneys" and the majority, in fact, were normal in size. 56% of their cases had smooth kidneys with little naked-eye abnormality, 23% showed fine pitting of the surface, and 21% had a finely granular surface. Fishberg describes it as the arteriolosclerotic kidney with the following characteristics: a usually adherent capsule but not always so, a variable degree of contraction, usually less marked than in the kidney of chronic glomerulonephritis, and a granular surface that may be coarse or fine.

On section, the kidney is firm and tough. The cortex is thin and poorly demarcated from the medulla. The cortical markings are obscured and irregular scarred areas descend into the medulla from the fibrotic depressions on the surface. The arteries of the intermediate zone are enlarged, abnormally prominent, thickened, and rigid.

Microscopic: Ischemic glomerular atrophy is the outstanding characteristic of these kidneys. The glomeruli are not uniformly involved in the ischemic process and a variable number appear normal. When ischemic atrophy is advanced, the surviving glomeruli are often slightly hypertrophied. All stages of ischemic glomerular atrophy may be encountered and the glomeruli so found tend to be grouped in foci throughout the cortex either in wedge-shaped areas beneath the renal capsule or in radiating streaks along the course of the interlobular vessels and their branches. In advanced stages, these streaks form an anastomosing network throughout the cortex with intervening areas of normal parenchyma.

The process by which ischemic glomerular atrophy occurs is roughly as follows:

The first change is a collagenous thickening of the basement membrane of Bowman's capsule at the pole opposite the glomerular hilum. A collagenous crescent is then formed in this region, bounded externally by the thickened basement membrane and internally by the unchanged parietal epithelium. The collagenous fibrils of the crescent coalesce to form a dense demilune stained deep red with Van Gieson's stain. At first, the tuft appears normal and filled with blood, but as the collagenous crescent forms, the glomerulus begins to shrink. The endothelial cells of the tuft disappear gradually with collapse of the capillary lumina, but the capillaries of the hilum remain patent until atrophy is very advanced. At this stage, the thick collagenous crescent is in contact with the periphery of the tuft. The final stage is one of distortion and disintegration in which the fibrous crescent is broken into segments and the intervening gaps invaded by small lymphocytes. The tuft disappears entirely so that all that remain are crescentic laminated areas of collagen lying amongst collections of

lymphocytes in the peripheral parts of the cortex. In short, this entire process is one of gradual infarction of the glomerulus by obstructing the afferent arteriole that supplies it, a process of "ischemic atrophy".

Accompanying the glomerular atrophy, the neighboring tubules also undergo severe atrophy, usually considerably in advance of that present in the neighboring glomeruli. The epithelial cells of the atrophic tubules undergo fatty degeneration and their lumina contain fatty or hyaline casts. The non-atrophied tubules show albuminous degeneration.

Associated with the glomerular and tubular atrophy is a dense, focal, hyaline fibrosis of the interstitial tissue. The fibrosis is composed of thick collagenous fibrils that seem to begin with a thickening of the basement membrane around the atrophied tubules. Sometimes these fibrotic areas are remarkably free from infiltration; in other instances, especially below the capsule, there is a dense infiltration with small lymphocytes and occasional plasma cells. No lipoid occurs in the interstitial tissue.

Arterial degeneration is a constant finding in these kidneys. The media of the interlobar, arcuate and interlobular arteries is hypertrophied. The intima is also hypertrophied. The most important and constant vascular change is a hyaline degeneration and occlusion of the lumina of the vasa afferentia of the glomeruli and the arteriolae rectae virae. This degeneration is secondary to hypertrophy of the media and intima of these vessels. In most instances, there is, in addition, fibrous degeneration of the hypertrophied media and intima of the larger arteries. The interlobular arteries undergo fatty degeneration.

Space does not permit of a discussion of the pathological changes elsewhere in the body. Hypertrophy of the left ventricle of the heart and of the muscular arteries throughout the body is the usual finding. As most of these cases die of cerebral haemorrhage or of cardiac failure, the usual pathological findings of these conditions are encountered.

Pathological Chemistry: The blood of the hypertensive patient commonly shows no abnormalities. Page, however, has been able to demonstrate recently the presence of a pressor substance resembling angiotonin in the blood of hypertensive patients. When heart failure complicates the picture, the blood N.P.N. will likely be elevated moderately.

Clinical Picture: The symptoms and signs of essential hypertension are conveniently described according to the manner in which they affect the different systems of the body. At first, of course, there are no symptoms, but sooner or later these appear in an insidious manner. The disease affects those in the age group of 40—60 years.

The patient may consult the doctor because of attacks of dizziness and buzzing in the ears. Often he complains of visual disturbances such as transient blindness and flashing lights before his eyes. Morning headache that awakens him at 4 a.m. is a common symptom. One day he may notice that an arm or leg becomes suddenly numb, tingling and weak. He may collapse suddenly on the floor with a transient paresis of one leg. Irritability, sleeplessness, and loss of power of mental concentration are very characteristic. Such a patient may one day go into a convulsive state of hypertensive encephalopathy as described under chronic hypertensive diffuse glomerulonephritis. The usual outcome is massive cerebral haemorrhage, coma and death. A few live for a time following a hemiplegia caused by cerebral haemorrhage, but sooner or later another haemorrhage carries them away.

The heart is commonly affected and may be the first vital organ to fail. The hypertensive patient begins to complain of shortness of breath on exertion that becomes slowly and progressively worse. Attacks of paroxysmal nocturnal dyspnea and pulmonary edema may occur. Physical examination commonly reveals an elevated blood pressure of say 180/100, enlargement of the left ventricle of the heart, and rales at the bases of the lungs. The right ventricle also may fail with the resulting development of venous engorgement, enlargement of the liver, ascites and massive edema. In the end stages, one commonly finds a gallop rhythm of the heart and total cardiac failure. Cardiac infarction is a not-uncommon occurrence in these patients, being about twice as common as in the non-hypertensives of the same age group.

It is a paradox that, although *post mortem* the kidneys always show changes in the afferent arterioles to the glomeruli, yet clinically very few die of uremia. Only about 8.16% die a uremic death, and it is likely that when this event occurs the termination is due to the development of "malignant" hypertension. Usually, there are no symptoms of renal inefficiency and few urinary abnormalities unless heart failure be present. The only common renal abnormality that could be attributed to the hypertensive changes in the kidney is the occasional excretion of a trace of albumin. Page, however, claims that, if sufficient care be taken, it is possible to demonstrate an early failure of hypertensives to maintain the renal blood flow and to concentrate the urine.

Lastly, mention must be made of the ocular fundi. Ophthalmoscopic examination commonly reveals a state of retinal arteriosclerosis only. When hypertensive neuro-retinopathy appears, one considers that the patient has entered the malignant phase of the disease.

Differential Diagnosis: This has been discussed above under hypertensive chronic diffuse glomerulonephritis, to which the reader is referred.

Prognosis: The ultimate outlook is uniformly bad, yet many hypertensive patients live for years even after a cerebral haemorrhage. Bell and Clawson found that, in their series of 420 patients, 187 died of congestive heart failure, 67 of coronary disease, 81 of cerebral hemorrhage and thrombosis, 49 of accident and intercurrent disease, and 36 of renal insufficiency. Christian's and Janeway's figures are in accord with these.

Treatment: There is, as yet, no satisfactory treatment for essential hypertension. Recently, anti-pressor renal extracts have been used in the treatment of hypertension, but have not as yet reached the stage of accepted therapy. Until we know the cause of essential hypertension, it is probable that we shall not find the cure.

Short of a cure, the best we can do is to regulate the patient's life according to the rule of moderation in all things. It is very important, if possible, to avoid worry and nervous strain. The judicious use of sedatives in the treatment of headache, dizziness, and sleeplessness is important. Cerebral haemorrhage and cardiac failure are treated as they arise, in the usual ways. Attacks of hypertensive encephalopathy are treated by venesection and, if necessary lumbar, puncture. At the same time, an intravenous injection of 50 cc. of 50% sucrose or glucose is indicated. The general plan is to protect the patient from extremes of all kinds, to insist on extra rest, to reduce weight if overweight, and to treat symptoms and complications as they arise.

B. Malignant Hypertension

Definition: A clinical syndrome characterized by the rapid development of extremely high blood pressure, fulminating cardiovascular hypertrophy and degeneration, and the terminal appearance of acutely progressive renal insufficiency.

Etiology: The cause of this syndrome is unknown, but it appears that it may arise in the following ways:

(*a*) *De novo*, in a short period of six months to a year in a previously healthy individual.
(*b*) As a terminal event in essential hypertension.
(*c*) As a terminal event in chronic diffuse glomerulonephritis.
(*d*) As a terminal event in chronic pyelonephritis.
(*e*) As a terminal event in eclamptic toxemia.

Pathology: Macroscopic: The kidney is moderately contracted with a capsule that is adherent to an even granular outer surface. The colour varies from grayish pink to reddish purple, according to the degree of congestion.

The cortex is uniformly narrow and the normal pattern is replaced by anastomosing strands of gray fibrous tissue. When the kidney is congested, the glomeruli appear as pinhead red dots. The demarcation between cortex and medulla is very blurred. The arteries are very prominent. In some cases the surface of the kidney is studded with small haemorrhagic areas.

Microscopic: A considerable number of the glomeruli appear to be normal while a minority are completely disorganized. Proliferative glomerulitis is absent while occasional slight proliferative capsulitis may be found. Adhesive glomerulitis and focal necrosis are constantly present. Ischemic glomerular atrophy is always present and conspicuous and predominates over toxic glomerular changes. There is reason to believe that this ischemic glomerular atrophy really represents a relatively acute infarction of the affected glomeruli and that it is due to the characteristic change that occurs in the corresponding afferent arterioles, namely, acute necrosis and fatty, hyaline degeneration.

The interstitial tissue undergoes a process of patchy reticular fibrosis. Large trabeculae of dense fibrous tissue contain, within their collagenous fibres, groups of greatly atrophied tubules. Between these trabeculae lie large islands of tubules that are either normal or show a regenerative hypertrophy.

The tubular epithelium undergoes albuminous and occasionally hyaline degeneration. The lumina contain a moderate number of erythrocytes and collections of neutrophilic leucocytes.

Inflammatory infiltration of the interstitium is sparse and is more focally distributed. The predominant cell is the small lymphocyte, although an occasional plasma cell and neutrophile may be seen.

The vascular changes in the cortex are striking. Both the media and intima of the arteries and arterioles are greatly hypertrophied. The larger arteries show secondary fibrotic degeneration of these coats. The vasa afferentia, as described above, are often obliterated as the sequel of necrosis and fatty, hyaline degeneration of their walls.

Very marked cardiovascular hypertrophy is a constant finding in these cases. The left ventricle of the heart is very thick and all muscular arteries show marked medial hypertrophy. Degeneration of the arterioles is found also, microscopically, in the spleen, pancreas, liver, brain, gastro-intestinal tract, and myocardium. Kernohan, Anderson, and Keith found medial hypertrophy of the arterioles of the voluntary muscles.

Pathological Chemistry: The blood of these patients shows the characteristic chemical changes of renal insufficiency progressing rapidly to those of true uremia.

Clinical Picture: These patients are usually men in their forties and, as stated above, they are subject to a rapidly progressive fatal disease in which very high blood pressure, cardiac embarrassment, and renal failure are the characteristic features. Reference has been made to the manner in which this fatal syndrome may arise. Irrespective of whether it arises *de novo* or by complicating and terminating some other disease, there can be no mistaking the symptoms. The patient goes downhill very rapidly with the development of great weakness, severe headache, blindness, dyspnea, and finally uremia and death. Although the majority of the cases die of renal failure, heart failure sometimes plays a conspicuous and even dominating part in the picture.

The ocular fundi show marked hypertensive neuroretinopathy with papill-edema, retinal haemorrhages, cotton-wool exudates, a macular star and severe degenerative retinal arteriosclerosis. The heart is greatly enlarged and commonly has a gallop rhythm. The blood pressure is extremely elevated to levels approaching 300/180. A variable degree of cardiac failure may be present, but it is usually inconspicuous. Often petechial haemorrhages are noted in the skin. Terminally, the picture is that of uremic coma as described above.

The urine characteristically has a low, fixed specific gravity with moderate albuminuria. Microscopically, red cells, pus cells, hyaline and granular casts are found. Renal function tests invariably show severe impairment of function.

Prognosis: The outlook is hopeless, with death occurring in six months to two years from the onset.

Treatment: There is no treatment that is of any avail in these cases. In a few early cases, splanchnic sympathectomy has been done with temporary improvement—notably in the Mayo Clinic.

CHRONIC PYELONEPHRITIS

In recent years, since the work of Parker and Weiss, we have come to include this disease under Bright's Disease because it can produce both renal insufficiency and hypertension with cardiovascular hypertrophy.

Definition: A chronic, ascending, non-suppurative inflammation of the interstitium of the kidney which results in fibrosis, hypertension and renal insufficiency.

Pathology: Macroscopic: In the absence of hydronephrosis, which may be present, the kidney is small, granular, and grossly or finely scarred. Each depressed scar represents a healed area of inflammation which resembles an old healed infarct. When the scarring is finer, the kidney may be indistinguishable from that of chronic diffuse nephritis. Both kidneys are commonly involved, but the disease may be confined to one side.

Microscopic: The glomeruli of affected nephrons show focal necrosis, adhesions, and occasionally proliferative capsulitis. periglomerular fibrosis produces hyalinized glomeruli which may disappear entirely.

The convoluted tubules undergo marked atrophy, while the collecting tubules contain numerous neutrophilic leucocytes.

In the late stages, some of the scarred areas contain groups of greatly dilated tubules with flattened epithelium. The lumina are filled with colloid-like casts so that the tissue resembles thyroid gland. It is probable that these casts represent the fused nuclear material of accumula-

tions of neutrophilic leucocytes. Decreasing numbers of leucocytes are present in the fibrous interstitium which is patchy or moderately uniform in distribution.

The arteries in the scarred areas show intimal hyperplasia with narrowing of the lumina. The arterioles show hyperplastic sclerosis with thickening of the entire wall and narrowing of the lumen. The inevitable result of these vascular changes is renal ischemia and arterial hypertension.

Pathological Chemistry: As in former examples of Bright's Disease, renal failure may occur with resulting nitrogen retention. More often, there is no chemical abnormality.

Clinical Picture: The usual story of these patients is that of an antecedent attack of acute pyelonephritis at some time in the past and the subsequent development of hypertension. Occasionally, they may be discovered by the occurrence of urinary frequency and the finding of albuminuria and pyuria. It may be almost impossible to distinguish them from patients with chronic diffuse glomerulonephritis. Usually radiological investigation by means of pyelograms is necessary to establish a clinical diagnosis. A marked radiological abnormality in one or both kidneys is of assistance in establishing the diagnosis. The usual symptoms and physical signs of hypertension and renal failure may occur in these as in other forms of Bright's Disease.

Prognosis: If the disease is unilateral, the prognosis is good, because the diseased kidney can be removed by the surgeon. If the disease is bilateral, the prognosis is the same as that of chronic diffuse glomerulonephritis, that is, poor.

Differential Diagnosis: The disease must be differentiated from chronic diffuse glomerulonephritis and essential hypertension. The distinction may be very difficult but is made on the characteristic histories and the radiological findings.

Treatment: If the disease is unilateral, nephrectomy is performed; if bilateral, the treatment is that of chronic diffuse glomerulonephritis.

Conclusion

It will be clear from the foregoing account that Bright's Disease is an extremely involved and difficult subject. Although much has been learned, much remains still to be discovered. It is probable that all forms of chronic Bright's Disease, in which renal sclerosis occurs, are subject to a vicious cycle which tends to cause progressive deterioration of the patient's condition and death from hypertension with cardiovascular hypertrophy and degeneration, or from renal insufficiency and uremia.

Acknowledgement

The author wishes finally to acknowledge with thanks his indebtedness to Dr. H. K. Detweiler, whose encouragement and helpful suggestions were of the greatest assistance in the revision of this paper.

BIBLIOGRAPHY

Russell, D. S.: *A Classification of Bright's Disease*, Special Report Series No. 142, Medical Research Council of Great Britain, 1929.

Fishberg, A. M.: *Hypertension and Nephritis*, Lea and Febiger, 4th Ed., 1939.

Hadfield, G. and Garrod, L. P.: *Recent Advances in Pathology*, Churchill, 4th Ed., 1942.

Boyd, W.: *Changing Concepts of Pyelonephritis*, Canad. M. A. J. **47**; 128 (Aug., 1942).

Lewis, A., and Goldblatt, H.: *Studies on Experimental Hypertension*, Bull. New York Acad. of Med., **18**; 459 (July 1942).

Page, I. H.: *Studies on the Mechanism of Arterial Hypertension* (Clinical Lecture at Atlantic City Session) J.A.M.A., **120**; 757 (Nov. 1942).

A PROBLEM IN DIAGNOIS

MISS H. A. PATRICIA MARCROFT AND ROBERT W. VAN DER FLIER, 4T9

PRESENTATION OF CASE

J. L., a thirty-year old, white male was transferred from another hospital to the Toronto General Hospital on May 15, 1948 for the investigation of generalized edema and right-sided pleural effusion. His chief complaint was shortness of breath.

This patient was in good health until early in March 1946 when he suffered a sore throat, headache and fever. These symptoms subsided after a week and he returned to work. During the last week of the same month, however, reddish, slightly swollen blotches appeared on his lower legs. They were 2-3 cms. in diameter, tender, painful and hot. Fever was present and was accompanied by some aching in the joints. He was admitted to a hospital and the diagnosis of erythema nodosum was made. At that time, radiological examination of his chest showed a shadow in the right lung apex and bilateral hilar densities and pulmonary tuberculosis was diagnosed.

On May 22, 1946, he was admitted to a sanitorium where sputum and gastric lavage examinations by direct smear and by culture were negative for tubercle bacilli. A positive specimen was obtained, however, from the right bronchial tree by bronchoscopy. The lesion in the right apex spread and an area of opacity developed in the left lung. Artificial pneumothorax was instituted on the right side in July 1946. He made satisfactory progress under such treatment and was discharged in June 1947.

During July 1947, a pleural effusion developed on the right side and 200 cc. of clear, straw-colored fluid were aspirated. The patient was treated in another hospital from August 1947 to May 1948, when he was transferred to the Toronto General Hospital. At the other hospital, fluid aspirations from the right chest were done once or twice weekly and, at first, 200-400 cc. of fluid were removed each time. By December 1947, however, the amount had decreased to 30-50 cc. The pneumothorax was discontinued in September 1947. During January 1948, the amount of the right pleural effusion increased until weekly aspirations of 1000-1500 cc. were necessary. At the same time, the patient began to notice dyspnea on slight effort, such as walking across the room. This became increasingly pronounced until by April, he was constantly short of breath even while at rest in bed and he obtained only partial relief following thoracentesis. Beginning in February 1948, edema developed progressively to involve first his ankles, then his legs and thighs, and by May, it extended up to the level of his axillae. Puffiness of his face was observed occasionally. He noticed increasing general weakness and anorexia. He gained 20-30 pounds between February and May. At no time did he have any precordial pain or hemoptysis.

This patient gives no history of rheumatic fever. He had jaundice when he was 2 years old, and chicken pox, whooping cough and measles during his childhood. In 1932, at the age of 14 years, he had acute anterior poliomyelitis which affected his back and both lower limbs, the right more severely. This was followed by a good recovery of function. There is no history of known exposure to or contact with tuberculosis. His family and personal histories are noncontributory.

On his admission to the Toronto General Hospital, May 15, 1948, he was found to be slightly dyspneic and cyanotic whether sitting up or lying flat in bed. His temperature was 100° F.; his pulse rate, 90; and his blood pressure 90 mm. systolic, 65 mm. diastolic. The jugular veins were distended for at least one inch above the clavicles. Examination of his respiratory system revealed: (1) a slight shift of the trachea to the left, (2) decreased excursion of the right side of the chest, (3) marked dullness on percussion over the right chest, below the third interspace anteriorly and the level of the sixth thoracic spine posteriorly, (4) reduction of tactile and vocal fremitus and distant breath sounds over the same area. The apex beat was neither visible nor palpable and the heart was not enlarged to percussion. The heart sounds were regular and no murmur or friction rub was heard. A paradoxical pulse was present with the blood pressure falling on inspiration and rising on expiration. The liver was enlarged. Its lower margin was 10 cms. below the right costal margin in the mid-clavicular line and 8 cms. in the mid-line. The spleen was palpable on deep inspiration, 4 cms. below the left costal margin. Some free fluid was present in the peritoneal cavity. Gross edema of the ankles, legs, thighs, abdominal wall and chest up to the nipple line was noted along with edema of the scrotum. There was some atrophy of the muscles, and weakness of the plantar- and dorsi-flexors, of the right leg. The knee and ankle reflexes were absent on that side. There was no clubbing of the fingers.

Laboratory examinations revealed no abnormal findings in the urine, a hemoglobin of 96%, a red-cell count of 4,800,000 and a white cell count of 9,000 including 65% neutrophiles and 25% lymphocytes. The blood sedimentation rate was 17 mms. at 1 hour. The non-protein nitrogen level was 38 mgm. %. The total serum proteins were 4.8 gms. per 100 cc. with 3.1 gms. albumin and 1.7 gms. globulin per 100 cc. Bromsulphalein retention at 45 mins. was 16%. The arm-to-tongue circulation time using calcium gluconate was 17 secs. The venous pressure was 19.5 cms. Both the sputum and the pleural fluid were negative for tubercle bacilli by direct smear and by culture. Fluoroscopic examination showed a large right pleural effusion and gave the impression of diminished amplitude of heart contractions. The electrocardiogram showed low voltages in all leads.

SUMMARY. The problem for diagnosis presented by this case is that of a thirty-year old man who, seven months after discharge from a sanitorium, began to complain of (1) dyspnea only partially relieved by aspiration of a right-sided hydrothorax and (2) generalized edema. Investigation showed that he had signs of greatly increased pressure in the great veins without cardiac enlargement or signs of valvular disease and accompanied by a slight reduction in the serum protein level.

DIFFERENTIAL DIAGNOSIS

In considering the differential diagnosis of this case, it is necessary to explain dyspnea, increased systemic venous pressure and generalized edema in the absence of obvious signs of heart disease.

The *nephrotic syndrome* is suggested by the serum protein level but it is excluded by the increased systemic venous pressure and the negative urinary findings.

Cirrhosis of the liver is suggested by the enlarged liver, the free fluid in the peritoneal cavity and the dependent edema but it is excluded by the in-

creased systemic venous pressure. A decrease in the serum albumin level may be observed in cirrhosis but it also occurs in constrictive pericarditis.

Heart disease with right ventricular failure is suggested by the increased systemic venous pressure, the generalized edema and the right pleural effusion but is excluded by the normal size of the heart, the absence of heart murmurs, the normal blood pressure, the improbability of atherosclerosis in a man of this age and the fact that he could lie flat in bed without any increase in his distress.

Constrictive pericarditis is suggested by the presence of an increase in systemic venous pressure with a normal-sized heart, the electrocardiographic picture of low voltages in all leads and the fluoroscopic impression of a decrease in the amplitude of cardiac contractions. The presence of pulmonary tuberculosis suggests that the constrictive pericarditis, if present, is of tuberculous origin.

CLINICAL DIAGNOSIS

Constrictive pericarditis, probably of tuberculous origin.

TREATMENT AND CLINICAL COURSE

The patient was placed on a regimen consisting of a high-protein diet providing only 1.0 Gm. of salt per day and the intravenous administration of a mercurial diuretic 2-3 times weekly. In response to this, there was a considerable reduction in the amount of edema and a loss of over ten pounds in his body weight. The serum protein level rose to 6.0 gms. per 100 cc. with 4.0 gms. albumin and 2.0 gms. globulin per 100 cc. The right pleural effusion required aspiration only at the time of admission.

A pericardiectomy was done on June 9, 1948. The pericardium was found to be thickened and adherent to the entire surface of the heart and the great vessels. It was stripped off of the anterior surface and part of the lateral surfaces of the myocardium. Two small pockets of pus were encountered during the operation. Pathological examination of the pericardium showed active tuberculous granulation tissue and, on direct smear, the presence of *M. tuberculosis*.

It was anticipated that an immediate improvement would not follow this operation because the tuberculous process was active in contrast to other cases of constrictive pericarditis treated by this method where fibrous scarring had predominated. The jugular venous pressure decreased but did not return to normal. During the time he remained in the Toronto General Hospital following operation, repeated aspirations of a left-sided pleural effusion were necessary. The liver and spleen remained enlarged. He was discharged to sanitorium in August 1948.

A report from the sanitorium, dated October 2, 1948, states that he is now free of complaints. He has no edema or other signs of increased venous pressure except that the liver edge is palpable 8 cms. below the right costal margin. There is no distention of the neck veins and the pleural effusions have completely resolved.

ACKNOWLEDGEMENT

The valuable assistance of Dr. R. F. Farquharson, Dr. J. Hepburn and Dr. H. E. Pugsley during the preparation of this case report is gratefully acknowledged.

DIETARY CYSTINE IN RELATION TO THE EFFECTS OF LIPOTROPIC AGENTS*

PHILLIP S. ROSEN, B.A., 5T2

The Phenomenon of fatty infiltration of the liver has interested scientists and clinicians for some time. It is found in such clinical conditions as diabetes, pernicious anemia, chronic alcoholism, tuberculosis and, not uncommonly, extreme obesity. The frequency of its occurrence has initiated much experimental work during the past thirty years. As a result, a better understanding of fatty infiltration together with a greater knowledge of fat metabolism has evolved. In recent years, there has been a great deal of interest aroused by the lipotropic agents, which prevent the accumulation of or remove excess fat in the liver, and the factors affecting their action.

Since the discovery that amino acids could be isolated from protein hydrolysates, the effects of the various amino acids on body function have been studied. In 1927, cystine was observed to produce fatty infiltration and degeneration of the liver parenchyma when added to a low protein diet (1). In other words, cystine has an antilipotropic action. During the next decade, this observation was verified by the controlled experiments of several other investigators. A low protein diet supplemented with 80 mg. percent of cystine caused a fifty percent increase in liver fat as compared with that of control animals.

These discoveries led to further research and, in 1937, it was claimed (2) that methionine was lipotropic and that the lipotropic action of any protein could be accounted for by its relative contents of methionine and cystine; these two amino acids being antagonistic in action —cystine tending to deposit fat and methionine tending to remove it.

The Toronto group under Best (3) then noted that the methionine and cystine contents of casein, in themselves, did not explain that protein's lipotropic activity, because a mixture of methionine and cystine exerted an insignificant effect as compared with a casein supplement that provided the same amounts of methionine and cystine.

Subsequently, the researches on fatty infiltration of the liver became allied with those on organic sulphur metabolism when it was observed that the sulphur-containing amino acids, methionine and cystine, were essential to growth; and that the toxic effect of high cystine diets was related to the rate of growth. These observations received further confirmation when it was shown that the gains in weight and increases in liver fat were more pronounced in animals fed protein supplemented diets than they were in animals fed the free amino acids, cystine and methionine, in amounts equal to those contained in the protein supplements. This led to the suggestion (4) that the protein caused a new tissue formation which increased the need for methionine in the body, and thus made it less available as a lipotropic agent.

About this time, it was realized that there was a possibility of discrepancies arising out of the use of rats of different ages. When adult animals were used for experiments (5), they did not develop fatty livers to the same extent as did

*Adapted from a paper originally presented before the University of Toronto Physiological Journal Club, December 10, 1947.

young animals fed essentially similar diets. The explanation of this difference was based upon the need of the younger animals for methionine being for both growth and lipotropism; while that of the older animals being limited to its lipotropic activity. Thus deficiencies of methionine in young animals would result in even less methionine being available for lipotropic activity and, therefore, in fatty infiltration of the liver. From these observations it was postulated that, in adult animals, the content of methionine and cystine in a protein accounted for the lipotropic activity of that protein, and that in growing animals it did not.

All early experiments in this field failed to take into account caloric intake, nitrogen balance, and the dietary levels of the essential amino acids. In order to ascertain if these factors were pertinent, several experiments were conducted (6) in which the essential amino acids were added to a diet containing gelatin as the basal protein so that the actions of methionine and cystine under "true physiological conditions" could be studied. When the essential amino acids were added, the liver fat was almost doubled, and it was suggested that these amino acids improved the nutritional state. It was inferred that the lipotropic action of free methionine added to a basal diet which contained sufficient amounts of the essential amino acids to permit maximum growth should equal that of an equivalent amount of methionine fed as casein.

Studies on renal hemorrhage (7) showed that the sulphur-containing amino acids play a major role in the growth requirements of animals and that renal hemorrhage is usually accompanied by a fatty liver. It was thought that the two conditions were closely associated because cystine, when added to a basal hypolipotropic diet, increased the fatty infiltration of the liver and the incidence of renal hemorrhage. Furthermore the factors which prevent renal injury due to cystine, are the same as those which alleviate fatty liver lesions, namely methionine and choline.

The relationship of age, sex and weight to the incidence of these renal lesions was studied. Young female animals on a low-choline, cystine-supplemented diet developed lesions more slowly and less severely than did male animals. This fact and the observation that the males grew more than the females led to a further important experiment. Young male animals were fed basal diets supplemented with cystine, and the diet that proved lethal in the shortest period of time was noted. This diet was then fed to six groups of animals. The first group was allowed to eat *ad libitum;* but the food intake of the remaining five groups was restricted, each group getting less than the one preceeding it. The group feeding *ad libitum* grew at a very rapid rate and died within a few days. As the food intake decreased with successive groups, their growth and mortality rates decreased until, in the last group, there were no deaths but also no growth. From this, it was concluded that the sulphur-containing amino acids are essential to growth and that the toxic effect of a high-cystine diet is related to the rate of growth.

In all the hypolipotropic diets used in the early work, there was a deficiency of the sulphur-containing amino acids which are so essential for growth. When cystine was added to a diet deficient in these sulphur-containing amino acids, but otherwise adequate, growth occurred and, with it, a new demand for labile methyl-groups arose. The addition of cystine thus occasioned a deficiency of lipotropic factors, which

was manifest by hepatic and renal lesions.

These experiments indicated that there was no direct antagonism between cystine and methionine; but rather a correlation, because together they supplied the organic sulphur and labile methyl-groups needed for growth and lipotropism respectively.

During the time that the early experiments were being carried out, it was known that cystine and methionine possessed certain features in common. In 1939, the relationship between these two was clarified when it was demonstrated (8) that methionine could be converted to cystine with the aid of serine. This biosynthesis tended to render the concept of direct antagonism between methionine and cystine not too readily acceptable.

Early workers reported cystine to be antilipotropic in that it produced renal and hepatic lesions. The cirrhotic hepatic lesions in animals fed the hypolipotropic diet were increased by cystine supplements but lessened by choline. Certain workers (9) however, reported that combined supplementation by cystine and choline had a greater therapeutic effect than by choline alone. From this it appears that at least one type of hepatic cirrhosis results from a more advanced stage of fatty infiltration of the liver than that seen in the experimental fatty livers resulting from the feeding of hypolipotropic diets to rats.

In summary, it can be said that the antilipotropic activity of cystine can not always be demonstrated and that the failure to do so is attributable to the basal diet being adequate with respect to labile methyl-groups, organic sulphur, or both. It is only when the basal diet is deficient in both organic sulphur and labile methyl-groups that the so-called "antilipotropic" activity of cystine can be demonstrated.

REFERENCES

(1) Curtis, A. C., and Newburgh, L. H.: Arch. Int. Med. **39,** 828 (1927).
(2) Tucker, H. F., and Eckstein, M. C.: J. Biol. Chem. **121,** 479 (1937).
(3) Best, C. H., and Ridout, J. H.: J. Physiol. **97,** 489 (1940).
(4) Treadwell, C. R., Groothius, M., and Eckstein, M. C.: J. Biol. Chem. **142,** 653 (1942).
(5) Horning, M. G., and Eckstein, M. C.: J. Biol. Chem. **155,** 49 (1944).
(6) Lucas, C. C., Beveridge, J. M. R., and O'Grady, M. K.: J. Biol. Chem. **154,** 9 (1944).
(7) Griffith, W. M.: J. Nutrition **21,** 291 (1941).
(8) DuVigneaud, V., and Binkley, F.: J. Biol. Chem. **144,** 507 (1942).
(9) Gyorgy, P. and Goldblatt, H.: J. Exp. Med. **75,** 355 (1942).

GENERAL REVIEWS

Best, C. H. and Lucas, C. C.: Vitamins and Hormones, **1,** 1 (1943).
Jukes, T. M.: Ann. Rev. Biochem., **17,** 293 (1947).
McHenry, E. M., and Patterson, J. M.: Physiol. Rev. **24,** 128 (1944).

THE UNIVERSITY OF TORONTO

MEDICAL JOURNAL

(An Undergraduate Publication)

This journal is published six times during each session, between October and April, by the Medical Society of the University of Toronto, to serve as a medium for student expression and to bring to each student recent articles of scientific interest.

$2.50 per volume. **50c per copy.**

FACULTY ADVISORS

E. A. Linell, M.D.
J. H. Couch, M.A., M.B., F.R.C.S., F.R.C.S.(C.)
J. Hepburn, M.B., F.R.C.P.(C.)
H. H. Hyland, M.D., M.R.C.P., F.R.C.P.(C.)
D. Y. Solandt, M.A., M.D., PH.D.
B. F. Crocker, M.A., PH.D.

EDITOR-IN-CHIEF

W. G. B. Casselman, M.A.

ASSOCIATE EDITOR

M. L. Bunker, M.A.

ASSISTANT EDITORS

C. Ezrin A. Rapoport D. C. Harrison

EDITORIAL ASSISTANTS

R. F. Hetherington D. E. Yates, B.A.
S. L. Wax C. M. Godfrey
Miss J. H. Griffin, B.A.

FEATURES EDITOR

E. B. Fish

MANAGING EDITOR

G. A. Trusler

ABSTRACTS

Editor: Miss H. A. P. Marcroft

Assistant Editors:

G. L. Ralph A. Bernstein, B.A. F. Williamson

CIRCULATION

Manager: J. G. Robinson

Assistants:

M. J. T. Sedlmeir I. A. Mitchell
G. V. Secord Miss D. F. Burton

ADVERTISING MANAGER

B. Berman

Season's Greetings

Very soon, Christmas lights will be shining in windows everywhere. Once more, the spirit of the holidays will be in the air. In those gleaming lights will be a message of joy and cheer for a merry, merry Christmas and a happy, gay New Year. May your Christmas be a joyful one filled with pleasant times and happy memories.

As you enter the New Year, amid a pandemonium of whistles and bells, pause for a moment of serious thought and realise that it is another milestone in your life. A new year can never be taken for granted. It is a gateway to be entered reverently, with a prayer on your lips and courage in your heart.

Everyone is a born optimist, ignorant and innocent in his confidence that tomorrow will always be even better than today. What is another year to the young who have, as they believe, so many years in store? Time is a commodity of which they cannot imagine being bankrupt. You cannot be a spendthrift of time—it is not unlimited. Set high ideals for yourself and make every day of the new year count toward the attainment of those goals.

"Ideals are like stars; you cannot succeed in touching them with your hands, but like the seafaring man on desert waters, you choose them as your guides, and, following them, you reach your destiny." (Schurz).

"You cannot hope, of course, to escape from the cares and anxieties incident to professional life. Stand up bravely even against the worst. Your very hopes may have passed out of sight, as did all that was near and dear to the Patriarch at the Jabbok fold, and, like him, you may be left to struggle in the night alone. Well for you if you wrestle on, for in persistency lies the victory and with the morning may come the wished for blessing." (Osler).

Whatever the New Year is to be, it will be what you make it. May it prove a happy one—happy for each of you and for all the world.

HUMANISM AND MEDICINE

H. B. VAN WYCK

PART III

THE PRE-HELLENIC WORLD — THE VALLEY CIVILIZATIONS

Among man's earliest considerable experiments in civilization, those flourishing in the Mesopotamian plains and the Nile Valley hold the interest of western Europe inasmuch as the two—the Sumerian-Babylonian-Assyrian and the Egyptian—cultures passed on to the west a wealth of tradition and practical achievement.

Only the barest historical outline will be attempted here. In Mesopotamia, the story begins about 4500 B.C. with the Sumerians, a non-Aryan race, who settled in the valleys of the Tigris and Euphrates. These people developed a culture undisturbed until 2800 B.C. when a nomadic Semitic speaking people, the Akkadians, led by Sargon the Great, conquered and fused with the Sumerians. From then until the arrival of the Persians, the Mesopotamian peoples were dominated by Semitic races. Other tribes under Hammurabi, about 2,000 B.C., established the kingdom of Babylonia, which, in its turn, was overthrown by the founders of the greater Assyrian Empire about 1100 B.C. The climax of this new power was about the reign of Ashurbanipal (669-626 B.C.) and with the fall of Ninevah in 612 B.C. the great Assyrian Empire, at one blow, fell a prey to its successors the Aryan Persians under Cyrus. This point marks the disappearance of Assyria from history and the end of the first Mesopotamian civilization.

Since then, the country between the rivers has been successively governed by Persian, Macedonian, Roman, and Arab; but the pomp of Babylon and Ninevah has lain buried for three millenia beneath the drifting sands. None of the successors of Cyrus the Persian have attempted to replace, among the changeless peasants and nomads, those perished glories of the Mesopotamian plains.

In Egypt, of which the early beginnings were about the date when the Egyptians stabilized their calendar, 4000 B.C., its civilization ran a chronologically parallel course. It may occur to the philosophic mind to note that this point of time—the beginning of the Fourth Millenium B.C.—from which the historian dates the formal beginning of civilization—is in the era in which our less enlightened forefathers placed the fabulous Garden of Eden, and even the least fanciful might be tempted to attribute this to a tenacious racial memory of a halcyon time of pastoral bliss before unhappy man forsook his native fields for the specious lure of the metropolitan slum.

Egypt had a much less chaotic history than Mesopotamia. Her invaders could not come at her from all sides, as obtained in the lands between the rivers, but she was vulnerable to invasion from the direction of the isthmus of Suez. Her long history is a succession of dynasties, most of them founded by internal factions although Babylonians, Asyrians, and Abyssinians had their turns as conquerors. Finally, when the Thirty-first Dynasty fell to Alexander the Great in 332 B.C. the Egyptian civilization came to its close and the country was then to be ruled by foreigners, first the Greeks, then the Romans, the Arabs, the Turks and last of all the British.

These two river civilizations had much in common. Each developed in a fertile valley, with a great river basin

to serve as a line of communication. These plains were an annual source of wealth which a turbulent history and the feet of conquering armies could never permanently destroy. Both developed under despotic conquerors whom, eventually, a supporting priesthood elevated to the rank of dieties ruling theocratic states. In each, the priestly order, which not only helped to maintain but also enjoyed the protection of the reigning caste, derived stability and privilege from a mutually advantageous alliance with the throne of despots. Thus, in the accumulation of temple wealth, even if the priesthood flourished by the impoverishment of the peasant, this early form of social inequality was compensated to some extent by the devotion of the priests to the study of the heavens, the growth of agriculture, and the birth of their rude sciences.

Perhaps also in both valleys in the earlier stages of these periods, we owe the beginnings in measurement, calculation, and writing to the more studious among the priests. That this monopolistic control of the early science and arts of man was perhaps directed mainly to the support of a theocratic state, detracts in no way at this stage of civilization from its value to mankind; as the early germination of the seeds of learning required in the chaotic centuries of the ancient world, the protection of both opulence and superstition.

Until the coming of the Greeks, these two civilizations moved in equally slow tempo to the contemporary world of the Far East; and, until that tempo quickened in the Fifth Century B.C., the line that has since divided the nations of the world into civilized and barbarian peoples had not appeared. Yet, even in these static millenia, the change from early freshness to ultimate rigidity in artistic conception delineates the change from the fine freedom of youth to the fixed and often extravagant conventions of age.

The priests were perhaps the only teachers of these ancient realms and among their disciples in the metropolitan centers of Thebes and Babylon, the arts and crafts including a rudimentary medicine found a fruitful origin. Both civilizations transmitted much of their culture to Greece through empires on their borders. The Minoan (Cretan or Aegean) Empire was a useful channel from Egypt to Hellas and similarly the Hittite Empire in the Highlands of Asia Minor served to pass the culture of Nineveh and Babylon to the Ionian cities of the Mediterranean sea coast.

The useful art of writing was developed in these valleys—the hieroglyphs of the sacred writings of Egypt and the cuneiform alphabet of the Sumarians and Babylonians. These are discoveries to the modern world within the last century; and, in their interpretation, the origin of the alphabets of modern Europe has at last been traced and brings us nearer to the ancient river dwellers than was the "father of history". When Herodotus first reported these to his own folk two thousand years ago, their message was illegible and remained so until the past few decades.

A last picturesque contrast may be noted. Whereas in Mesopotamia, clay remained alike the medium for the recorder, the potter, and the architect, and the archeologist requires the spade to disclose the vanished past; in Egypt, vast piles of ordered masonry remain above the surface of the land still defying the ravages of time and the sands of the desert.

Such were these two static civilizations which were old when Greece was young. In these ancient lands, the thought of the time was dominated by a primitive religion and a superstitious

priesthood. The progress made by the pioneer intellectuals in Thebes, Ninevah and Babylon was stimulated by the needs of agriculture, irrigation, and navigation and many traces of this have come through to the present. From the Babylonians, we accept the week of seven days and the hour of sixty minutes; and perhaps, the religious and astronomical relations implied in the names of the days of the week have the same origin, names in each case in our western languages suggesting a deification of the stars and planets. The points of the compass governed the architecture of these ancient peoples; in this the pyramids of Egypt built about 3,000 B.C. are examples of impressive accuracy. The Egyptians were keen observers of the heavens, and the coincidence of the conjunction of the rising of Sirius and of the sun was found to mark the coming of the Nile flood. Both in Egypt and Babylonia did the practical needs of the people initiate the prediction of astronomical phenomena; and, as this is seen in the construction of temples, it suggests that this rudimentary science was fostered and, no doubt, exploited by the priestly cults. The practical needs of the restoration of boundaries of the fields of the Nile valley, ill-defined after each annual inundation, brought forth the science of geometry. In its early Egyptian form, it was uninvolved by theory and devoted to the areas of squares and triangles of agricultural land. To the Egyptian mathematicians of 2000 B.C. the calculation of the area of a circle by squaring the diameter reduced by one ninth sufficed. Greater accuracy awaited the discovery and use of the algebraic symbols required. Egyptian mathematics were simple and directed to concrete use. Our meagre knowledge of their rudimentary trigonometry and algebra derives from the Rhind papyrus (1600 B.C.) in the British Museum.

Medicine which has often fostered the growth of the biological sciences seems to have developed in a rudimentary stage early in the history of all civilized peoples. The medical lore of Egypt survived in the papyri written, treasured, and recopied by the priest class. Much of this lore became ultimately known to Hippocrates and his contemporaries of the Periclean Age. There was no doubt an association between the lore by which bodies could be kept from putrefaction, the transcendental vision of the immortality of the body, and the rude elements of hygiene. Before the dawn of history, trephining, done most probably for superstitious reasons such as the release of the insane spirit, cupping, circumcision, castration, venesection were all done by primitive peoples and there is evidence that in the civilized Egypt of 2500 B.C. these were standard procedures.

In the records of therapy found in the London papyrus, the lesser Berlin papyrus, and Brugsch papyrus, mystical and magic rites prevailed, augmented by an overful pharmacopeia to be applied to ulcers, haematuria and diseases of the breast and heart. In the Ebers papyrus, compiled about 1600 B.C. there is less dependance in incantation and charms; and, in the listing and treatment of many diseases, most of which we can recognize (for example, such still locally prevalent conditions as hook worm disease or Egyptian chlorosis, and bilharziasis), there is evidence of a wider knowledge of anatomy, surgery and diagnosis than, as far as is known, had as yet been achieved.

The Egyptian relied on the preservative action of salt, wine and the aromatics in the art of embalming and gained some knowledge of the anatomy of the viscera and brain in their removal.

Much has been learned of the prevalence of disease by the examination of mummies; and it may be inferred that rickets and syphilis were absent, that pyogenic infections and dental caries were minimal and that the death rate of children was much lower in ancient than in modern Egypt. Arthritis deformans was common. Renal and vesical calculus were known as well as gall stones and calcareous blood vessels. Many cases of well set fractures have been found. Egypt was famous among the surrounding nations for its skill in medicine. In the Odyssey, one reads of Egypt where the physician with a multitude of drugs is wiser than other men; Jeremiah alludes to its fabulously rich pharmocopeia; and Herodotus, referring to the Egyptians of the Fifth Century, speaks of the specialization of medical lore among the practitioners and of the rigorous personal hygiene of the priestly caste.

In the practical techniques of metal work, the smelting of iron ore, which was practiced as early as 3500 B.C., the weaving of cloth, the making of soap, glass, enamel and ceramics, the Egyptians were brought to a high state of efficiency. These considerable practical achievements were unmatched by speculative advance; and the gradual eclipse of their civilization by the armed conqueror without and the dead hand of slavery from within, has left a memory of perished material magnificence. The monuments thereof remain today in piles of stones among a decadent race whose days of greatest glory contributed little beyond methods of exquisite craftsmanship and a few instances of applied science. Much of this filtered across to Greece both indirectly by contact with the Mycenean civilization and by direct transmission through trade relations. Conspicuous among the many travelling observers were Herodotus and Plato.

Since 1843, excavations in Babylonia and Assyria have disclosed parallel civilizations whose scientific achievements were practical rather than speculative and intellectual, and again the chief exponents were temple priests. The Babylonians appear to have had a more systematized knowledge of astronomy than the Egyptians. The length of a year and the month, the movements of heavenly bodies, and the recurrence of eclipses, meteors and comets received careful study. Their findings became the groundwork of the pseudo-science of astrology; and, in the prediction of events by observation of the heavens, early peoples testified, by false inference, to a faith in cosmic law. In mathematics, they developed systems adequate to their needs in astronomy, commerce, and agriculture. They devised a decimal system, and divided the circle into 360 degrees. Babylonian design and construction reveal a considerable knowledge of geometry. The crafts were highly developed. Tin, copper, lead, glass, silver and gold were employed; sculpture and architecture had impressive development; and the life of the privileged ruling class and temple attendants reached an advanced stage of material comfort.

The early record of medicine in Babylonia did not impress the Greek observers of the 5th Century and reveals a prevalence of superstitious beliefs. The priests studies the entrails of sacrificial animals in order to divine the thoughts of the gods—a practice which, while impressing the credulous, must have stimulated the curious to form anatomical concepts. In a code drawn up in the reign of Hammurabi (2100 B.C.) a contemporary of Abraham, the operation for cataract is mentioned, with the interesting clause that, if unsuccessful, the loss of the patient's sight demanded the amputation of the guilty surgeon's hands.

The far from perfect records of these ancient peoples of the Mesopotamian and Nile valleys hold a tale of material and practical achievements. These brought about social developments with the resultant increase in population. From the primitive kinship-basis of social life, the political integration of larger social units permitted the development of the two extremes of society—the privileged leisure class and a slave caste devoted to manual labor—with an intervening stratum of industrial and professional craftsmen. With the appearance of this differentiation of caste, tribal community gave place to civil society; war increased its scope by conquest; and the dominating trait of this ancient world was the tendency to hold a homogeneous culture intact by religious and military coercion. Supernaturalism and intolerance marked its zenith and as its civilizations passed into decline, they were ripe to pass on to their successors the social traditions of caste, despotism, the stirrings of a religious instinct overlaid with superstition, and a pandora of material achievement and practical, if primitive, science.

Such a society was not fertile ground for the growth of humanism and, as yet, the intellectual and spiritual aspirations of man which require the free exercise of the curious and skeptical function of the human mind, had not begun their persistent, if at times intermittent, search for fulfilment. For this, an epochal step forward of the human race, and more especially of our western society, fate was preparing a peculiar instrument, a people whose environment, opportunity and native genius in less than two centuries of incandescent intellectual and political activity set the western peoples on a new path and altered the destiny of the world.

When the light of history finds a new focus on the market places of the Greek world of the Fifth and Fourth Centuries B.C., we find that our gaze which had been centered on the remote and dimly lit stage of the Near East, at first is now blinded by the perception of a clear, brilliant, and credible scene with actors who, unlike the dim shadows that pass through the story of the more ancient East, are real people similar to ourselves in needs, emotions, and reaction to life. The Assyrian or ancient Egyptian as he trys a vain communication to us across the centuries presents an unreal form and speaks with a tongue that is alien. Of the Greek of the Age of Pericles, we we read the records, the lineaments of his features are familiar and well remembered, and his speech is our own. And now we leave these old river valley civilizations —slow moving throughout four millenia—and pass to the quickening life of the Greek peoples.

We must note that as the Greeks were settling about the Aegean, another group of tribes of Semitic birth began to occupy the narrow strip of territory they still call their homeland. Both the Greeks and the Jews chose the hardest and narrowest areas in the Mediterranean basin and each race was destined to contribute to the human intellect and soul, new forces which would alter the destiny of the west and all mankind.

Palestine, which though insignificant in population and political importance, was destined to give to the world one of its greatest literatures, two of its greatest religions and many of its profoundest intellects, was, for centuries, obscure in the shadows of declining despotisms. But as we approach Greece at the beginning of the Fifth Century B.C., the glory of the Great Age of Hellas was about to be born.

(*To be continued*)

ABSTRACTS

ANATOMY

The Parotid Gland in Relation to the Facial Nerve. J. McKenzie: J. Anat. **82,** 183-186 (July, 1948).

The author presents evidence that the facial nerve runs forward in the substance of the parotid gland as claimed by Gray and Cunningham. He refutes, however, the statement made by Bailey "that the parotid gland is a bilobed structure possessed of a large superficial and a small deep lobe connected by an isthmus; and that the facial nerve lying between the two lobes could be compared to the meat within a parotid sandwich."

He injected a suspension of India ink into the main parotid duct before dissection and identified each lobule by tracing tributaries of the duct along their whole length. He observed superficial and deep parts to the gland, connected not by one isthmus but by several with communications occurring through any gaps in the plexus of the facial nerve and not solely between the two main divisions of the nerve. The exact manner of interdigitation between nerve and gland is not constant, the gland resembling a creeper weaving itself into the meshes of a trellis-work fence.

The possibility of being able to define lobes in the living subject is difficult and the surgeon may get an erroneous impression due to the difficulty of distinguishing the ducts as they traverse the plane of the nerve.

Miss S. Ramcharan

HEMATOLOGY

The Life Span of the Megalocyte and the Hemolytic Syndrome of Pernicious Anemia. Singer, King and Robin: J. Lab. and Clin. Med. **33,** 1068-1076 (Sept., 1948).

In untreated pernicious anemia there is a shortened survival time of erythrocytes, and an abnormal elimination pattern, which becomes normalized after adequate administration of liver extract. With the extreme hyperplasia of the marrow which occurs, excessive urobilinogen output could be adequately explained on the basis of an increased rate of hemoglobin destruction. The demonstration of an abnormal life span of the megalocyte characterizes Addisonian disease as a true hemolytic syndrome.

The absence of any considerably increased reticulocyte count in untreated pernicious anemia indicates that replacement of erythrocytes occurs predominantly by means of non-reticulated megalocytes. Apparently completely matured although qualitatively abnormal corpuscles are released into the circulation. This is a distinguishing feature. There is speculation that the liver extract principle may contain a specific reticulocytogenic factor.

That pernicious anemia is a true hemolytic syndrome does not invalidate the concept that it is a deficiency disease. Lack of maturation principle permits defective erythrocytes to enter the circulation and be eliminated more rapidly than normal ones. There is then a hemolytic syndrome caused by an intracorpuscular mechanism, namely a poorly constructed erythrocyte cytoskeleton.

D. E. Yates

MEDICINE

Hyperparathyroidism. L. B. Burk: Am. J. Surg. **76,** 404 (Oct. 1948).

Ten cases are analysed with particular reference to early diagnosis. The most important symptoms were found to be: (1) Renal: colic, hematuria and calculi; (2) Skeletal: persistent aching pains in the back and lower limbs increased by weight-bearing, presence of bone tumours and cysts, spontaneous fractures; (3) Hypotonia, with persistent weakness and fatigue and (4) Gastrointestinal upsets. Laboratory findings were: (1) Serum calcium levels of 11.3 — 16.1 mgm. per 100 cc. with normal serum protein levels; (2) Serum phosphorus levels of 2.2 — 4.0 mgm. per 100 cc. (values are low unless renal insufficiency results in phosphorus retention); (3) Alkaline phosphatase levels of 3.9 — 19.5 Bodansky units — this estimation is of diagnostic value only in the presence of advanced skeletal disease because it is an index of osteoblastic activity; and (4) Secondary normocytic anemia may be present, resulting from replacement of hematopoietic elements by reticular cells. A positive diagnosis made early will prevent most of the crippling sequelae of long-standing hyperparathyroidism.

Miss A. I. Scott

Friedlander's Bacillus Meningitis Successfully Treated with Streptomycin and a Consideration of Friedlander's Bacillus Infections in Diabetes. L. F. Ayvazian: Am. J. Med. **5,** 449-461 (Sept. 1948).

The author reports a case of Friedlander's bacillus meningitis in which the therapeutic use of streptomycin successfully cleared the infection. Although sulphadiazine was used in conjunction with streptomycin, it was totally ineffective when used alone prior to the addition of streptomycin.

In 34 cases of Friedlander's bacillus meningitis in the literature, a total of 7 patients were known diabetics. In completely reported cases, 23% of all types of Friedlander's bacillus infections developed in diabetics. There is a close association between diabetes and Friedlander's bacillus infections especially in the disseminated or hematogenous, non-pulmonary types. In a total of 55 patients with a Friedlander's bacillus infection, 12 had a pulmonary infection while 43 had an extrapulmonary infection, such as meningitis, liver abscess and septicaemia.

J. I. Leventhal.

Vasoconstriction and the Development of Irreversible Hemorrhagic Shock. H. C. Wiggers, R. C. Ingraham, F. Roemhild and H. Goldberg: Amer. J. Physiol. **153,** 511-520 (June 1948).

Generalized vasoconstriction, reduced circulatory capacity and simultaneous redistribution of blood from so-called luxury organs to vital organs, following severe hemorrhage is fully recognized. This initial beneficial influence of vasoconstriction permits a greater loss of blood without the development of hemodynamic crises. However, continuance of severe vasoconstriction, in addition to the arterial hypotension incident to hemorrhage, may prove "deleterious".

Previously it had been shown that vasoconstriction increases in severity as impending shock (residual blood volume less than 60% of the prehemorrhage blood volume) progresses toward irreversibility, through the elaboration of humoral vasoconstrictor agents, thus further threatening the blood supply to large areas which already have been severely reduced by low arterial pressure and reflex vasoconstriction.

The investigators set out to demonstrate the deleterious influence of protracted vasoconstriction, by comparing the survival rates of a series of control dogs, with those of another group deprived of their sympathogenic vasoconstrictor mechanism. Dibenamine hydrochloride was employed to block this mechanism of both humoral and reflex origin. Initially, it was administered 30 mins. before bleeding, but cardiovascular conditions were found to be unstable at that time. A second group were treated with dibenamine 20 hrs. in advance to allow enough time for complete drug action, and for the compensatory adjustments to the cardiovascular influences of this drug.

In the control dogs 30% recovered, whereas in the pretreated dogs 60% recovered. The difference in recovery rate was the result of delaying the transition from impending to irreversible shock.

A. Bernstein

A Test For Adrenal Cortical Insufficiency. G. W. Thorn et al.: J. Amer. Med. Assn. **137** (12), 1005 (1948).

Two striking and easily determined changes consistently follow the administration of a single dose of 25 mg. of purified pituitary adrenocorticotropic hormone to normal subjects and to patients with diseases not involving the adrenal cortex. These are (*a*) a decrease in circulating eosinophiles and (*b*) a rise in the excretion of uric acid. It is suggested that a decrease of 50% or more in the urinary uric acid-creatinine ratio indicates an adequate adrenal cortical reserve. The test as outlined appears to be a measure of the adrenal reserve of hormones regulating carbohydrate, fat and protein metabolisms. The use of this test in the diagnosis of adrenal insufficiency is discussed.

Miss J. E. Wood

PATHOLOGICAL CHEMISTRY

Recent Developments in Water Balance. J. R. Robinson: Am. J. Surg. **76,** 383-392 (Oct. 1948).

Beginning with a consideration of definitions and general fundamental concepts, the author presents a review of water and salt balance with special reference to their implications in surgery. The etiologies and clinical pictures of various types of disturbances of extracellular water balance, the violations of modern fluid balance concepts, the mode of fluid administration and some specific examples of treatment in special cases are discussed.

G. L. Ralph

PATHOLOGY

Effect of Choline in the Prevention of Experimental Arotic Atherosclerosis. A. Steiner: Arch. Path. **45,** 327-332 (Mar. 1948).

The author fed cholesterol mixed with regular food daily to 54 rabbits; to 29 of these he also fed choline hydrochloride. The rabbits died or were killed 40 — 100 days after the beginning of the experiment and an autopsy was done on each to examine the extent of fatty change in the aorta and liver. During the experiment biweekly blood cholesterol estimations were made and in both choline-fed and control rabbits, a comparable progressive hypercholesterolemia was noted.

None of the choline-fed animals killed at intervals between the 40th and 80th days showed any macroscopic aortic atheromata. Ten of 11 control rabbits fed the same amount of cholesterol and killed in similar periods showed gross atherosclerosis. Two animals receiving 1 gm. of choline hydrochloride daily, which were killed after 90 days and two of five examined after 100 days were free of aortic lesions. The extent of atherosclerosis was less in those animals receiving choline in which aortic lesions developed after 80 days.

G. L. Ralph

Chronic Infection and Atherosclerosis. N. W. Jones and A. L. Rogers: Arch. Path. **45**, 271-277 (March, 1948).

Experimental data and clinical evidence are cited which suggest that atherosclerotic heart disease may in some cases be related to chronic infections, the causative organisms possessing an "elective" affinity for vascular tissue. In this report the site of chronic infection studied particularly was the paranasal sinuses. The authors have shown: (1) that a direct anatomical pathway exists between the paranasal sinuses and the paralaryngeal lymph glands and (2) that particulate matter (e.g. Trypan Blue) introduced into the paralaryngeal lymph nodes can be demonstrated in the phagocytic cells within the aorta and coronary vessels.

Using cats as experimental animals, they introduced micro-organisms into the paranasal sinuses or paralaryngeal lymph nodes and recovered them by culture from the walls of the aorta and coronary vessels and demonstrated them in stained sections of these tissues.

Cases are cited where surgical removal of chronically hyperplastic sinus tissue has brought about rapid compensation of a failing atherosclerotic heart which could not be recompensated by the usual therapeutic measures. It is suggested that such chronic infections might well be studied from the standpoint of their playing a direct or indirect part in the development of atherosclerosis.

R. F. Hetherington

PHYSIOLOGY

The Uptake of Glucose and the Synthesis of Glycogen by the Isolated Diaphragms of Normal and Pituitectomized Rats. M. Perlmutter and R. O. Greep: J. Biol. Chem. **174,** 915-924 (July 1948)

The authors undertook to show that "if the action of insulin is solely to release the inhibitory action of anterior pituitary extract on the hexokinase reaction, no effect of insulin *in vitro* should be found when diaphragms from hypophysectomized animals are used."

The diaphragms were removed from normal rats and rats pituitectomized 4-5 days previously. The initial glycogen contents of portions of the diaphragms were determined, using the method of Good, Kraner and Somogyi. The remainders were placed in a Warburg vessels and the amounts of glucose utilized measured by a modification of Benedict's method.

Their results do not support the assumption that the action of insulin is solely upon the hexokinase system. They found that the effect of insulin upon glucose utilization *in vitro* is as great in the diaphragms of the pituitectomized rats as in those of the normals. Insulin, therefore, directly increases the glucose utilization of the diaphragm even in the absence of the inhibitory effect of the anterior pituitary hormone.

Miss E. Toguri

PSYCHIATRY

The Psychotherapeutic Management of Functional Disease. H. Evans: Med. Arts Sci. **2**, 59-66 (April, 1948).

With increased scientific knowledge, there has been a tendency to treat the part and to ignore the total problem of the individual with a consequent increase in functional diseases. To treat these diseases the physician requires faith in the psychotherapeutic technique, interest in his patient as a person, objectivity in his regard of the patient's problems and knowledge of the psychodynamic concepts of mental function including the operation of the unconscious portion of the mind. The technique of psychotherapy, as can be practised by the general physician, is discussed.

A. C. Parkin

Gynaecological Psychiatry. L. Smith and B. Ridley: Br. Med. J. No. 4573, 418-421 (Aug. 1948).

During the two years of operation of a psychiatric clinic organized within the gynecological department of a general hospital, 165 patients were considered psychneurotic in varying degrees of severity. The most common complaints were frigidity and dyspareunia, secondary to either maladjustment to the husband or fear of pregnancy. The latter fear was associated in all cases with unsatisfactory contraceptive technique, coitus interruptus being most common. Marital maladjustment was related to earlier childhood relationships—the failure of emancipation either from parents or from childhood precepts and prejudices.

A. C. Parkin

SURGERY

The Indications for Emergency Operation in Severe Hemorrhage from Gastric or Duodenal Ulcer. J. E. Dunphy and S. Hoerr: Surgery **24,** 231-238 (Aug. 1948).

This article is the result of investigations carried out at the Peter Bent Brigham Hospital under the auspices of the Department of Surgery, Harvard Medical School. The vast majority of patients who bleed from the upper gastrointestinal tract will recover under conservative care. Some patients, however, will die if operative intervention is withheld and the problem is to recognize these cases before they are almost moribund and at a time when surgery will have its minimum mortality. The rate of bleeding, above all other factors, governs the outcome under conservative management. Arteriosclerotic arteries do not go into spasm so readily as do normal ones and, therefore, bleed more rapidly.

Operative intervention need not be considered when the hemorrhage is compensated, that is when syncope, shock and hypotension are absent. Critical evaluation of a patient in shock is essential. His initial therapy should be a whole-blood transfusion, usually 1-2 litres, which should then be continued at a rate of 500 cc. per each 8 hours. If the patient does well on this transfusion regimen, operation is not indicated. However, if he continues to lose blood at a rate greater than that of his transfusion, as evidenced by a return of signs of shock or by his responding well at first and then gradually losing ground over the next few days, his circulation should be restabilized by a further transfusion and then an emergency operation performed.

R. W. Van der Flier

Renal Tuberculosis—A Case History. J. B. Maxwell: Bull. Toronto East Med. Assn. **13,** (7), 1 (Sept. 1948).

The history of a case of early, bilateral renal tuberculosis, having hematuria as the sole indication, is presented. This case was treated according to the method described by Slotkin which depends upon the bacteriostatic action of streptomycin on *M. tuberculosis*, and upon the apparent solubility of the lipoidal "wall" of the organism in chaulmoogra oil. 1.0 cc. of chaulmoogra oil was administered intramuscularly, daily for 30 days. 125 mg. of streptomycin in 2.0 cc. of distilled water was administered intramuscularly, every 3 hours for the same 30 days. The patient suffered no untoward effects. At the end of the treatment period, cystoscopy showed that two tubercles in the bladder which were previously present had healed completely. Retrograde pyelograms indicated complete arrest of the pathological process in the kidneys. The urine remained free of tubercle bacilli for three weeks. Then, the smears became positive for *M. tuberculosis* for several weeks, following which the organisms have remained absent for one month, up to the time the article was written.

W. G. B. Casselman

RECENT ACCESSIONS TO THE MEDICAL READING ROOM

Biology of melanomas. (Special publications of the New York Academy of Sciences, Vol. 4). 1948.
British Medical Association, Medical Curriculum Committee: **The training of a doctor.** 1948.
British Pharmacopoeia. 1948.
Donaldson, J. K.: **Surgical disorders of the chest.** Ed. 2. 1947.
Gilmour, J. R.: **The parathyroid glands and skeletons in renal disease.**
Great Britain, British Information Services: **Health services in Britain.** 1948.
Josie, G. H.: **A report on drug addiction in Canada.** 1948.
Ruesch, J.: **Chronic disease and psychological invalidism.** 1946.
Wilson, C. W.: **Radium therapy; its physical aspects.** 1948.
Wright, R. D.: **A primer in clinical science.** 1948.

THEELIN:

continuing leadership in estrogen therapy

naturally occurring

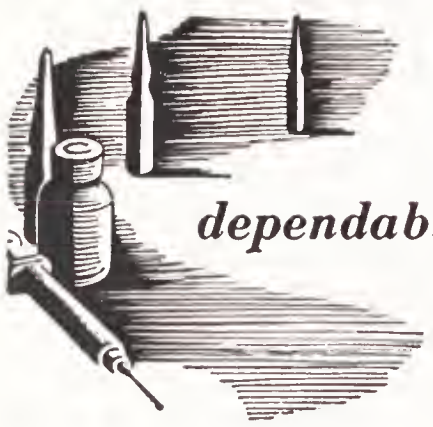
THEELIN is a *naturally occurring* estrogen It is well tolerated and can be administered without significant side reactions or untoward effects.

THEELIN is a *pure crystalline* estrogen. Since it is not a mixture and does not contain extraneous substances, its physiologic effectiveness is accurately determined by weight.

pure crystalline

THEELIN is a *highly potent* estrogen. One ten-thousandth (0.0001) of a milligram is equivalent to one international unit. Because of THEELIN's potency, symptoms of the menopause and other estrogen-deficiency states may be readily and effectively relieved.

THEELIN is a *dependable* estrogen. It has stood the test of time. The first estrogenic hormone to be isolated in pure crystalline form and the first to assume clinical importance, THEELIN may be depended on for its reliable and predictable estrogenic effects.



dependable

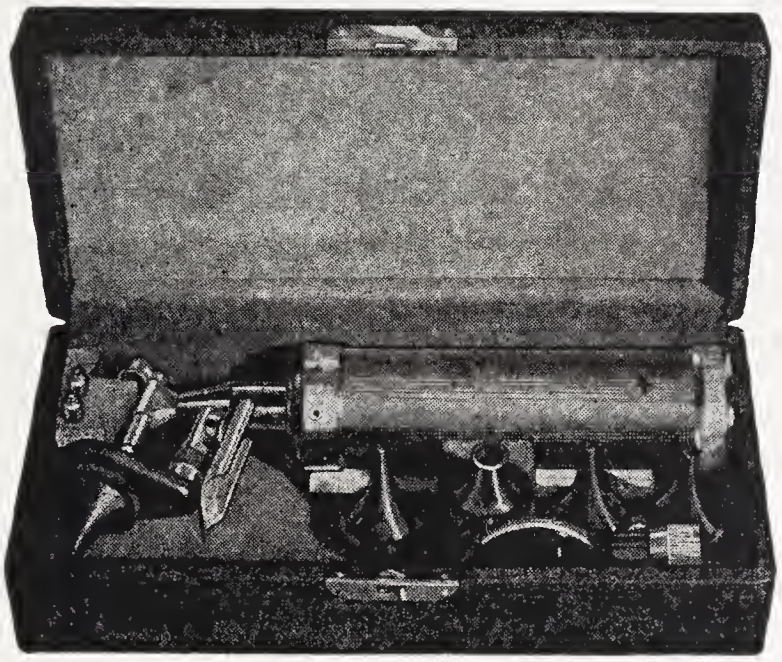
THEELIN is available as THEELIN AQUEOUS SUSPENSION in ampoules of 1 mg. (10,000 I.U.) and 2 mg. (20,000 I.U.)
THEELIN IN OIL in ampoules of 0.1 mg. (1000 I.U.) 0.2 mg. (2000 I.U.), 0.5 mg. (5000 I.U.) and 1 mg. (10,000 I.U.);
STERI-VIAL® THEELIN IN OIL in vials of 10 cc., each cc. containing 1 mg. (10,000 I.U.); and THEELIN Vaginal Suppositories, containing 0.2 mg. (2000 I.U.).

PARKE, DAVIS & CO., LTD. • WALKERVILLE, ONTARIO

MEDICAMENTA VERA

WELCH ALLYN OPHTHALMOSCOPE

With Illuminating and Lens System as devised by Dr. C. H. May



In addition has a Sliding Diaphragm Device giving

- SLIT APERTURE
- PIN HOLE APERTURE
- CLEAR APERTURE
- DAYLIGHT FILTER
- RED FREE FILTER

THE J. F. HARTZ COMPANY LIMITED

MONTREAL TORONTO HALIFAX

for **Quick Action!**

in the Respiratory and Circulatory Emergencies of Intravenous Barbiturate Anesthesia.

inject

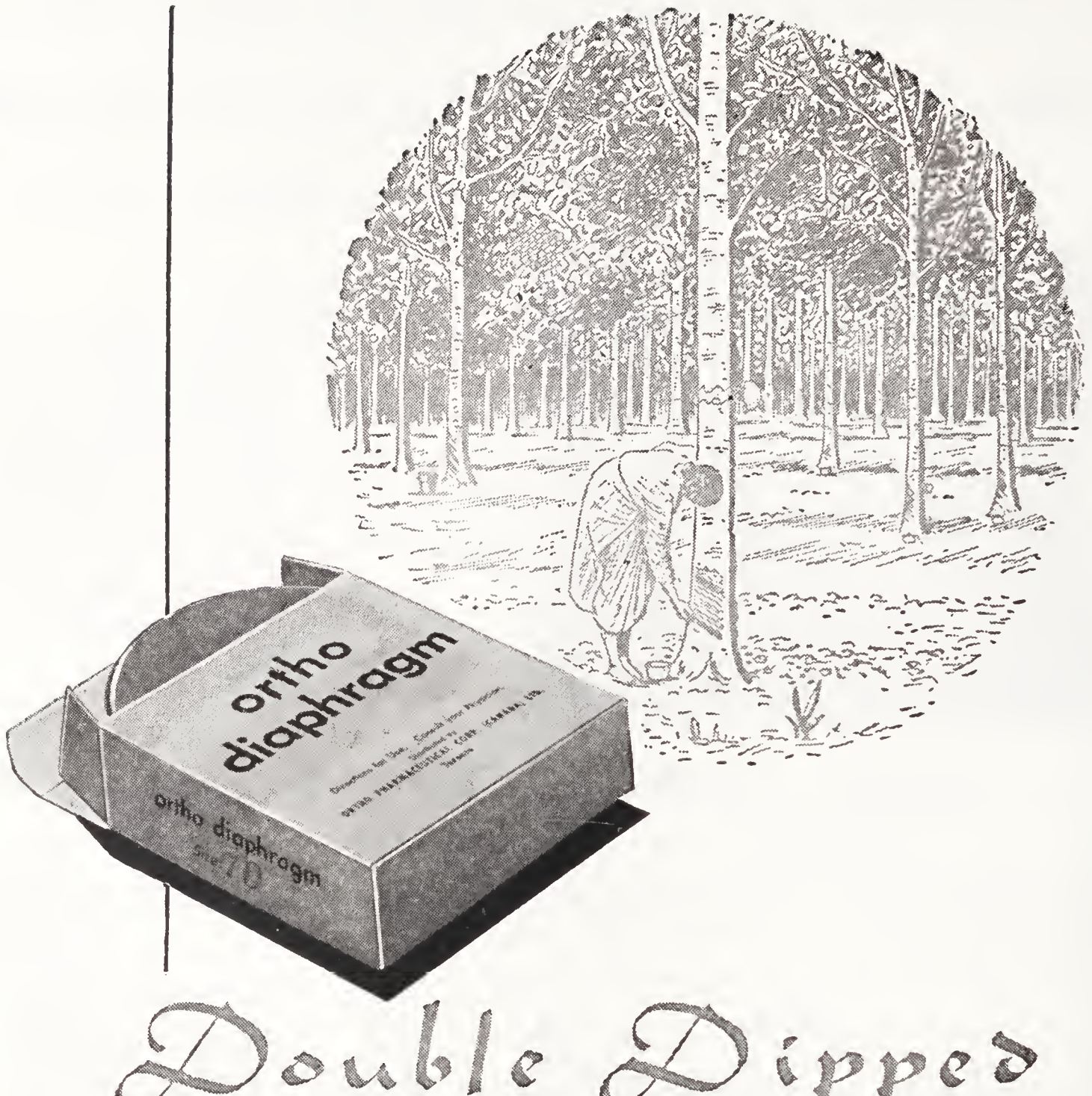
COUNCIL ACCEPTED **Metrazol**

intravenously, intramuscularly, subcutaneously

In respiratory and other emergencies resulting from medullary depression during anesthesia. Ampules 1 and 3 cc., tablets, solution, powder.

Metrazol, brand of pentamethylentetrazol, Trade Mark Reg. U. S. Pat. Off., E. Bilhuber, Inc., Mfr.

Bilhuber-Knoll Corp. Orange, N. J.



Double Dipped

FOR DOUBLE PROTECTION

Light, sturdy dome has two layers of Latex to insure absence of minute flaws. This double dipping of the Ortho Diaphragm prevents punctures . . . thus wear resistant, longer lasting. Individually packed . . . in sizes 55 to 100 millimeters . . . in the familiar Ortho blue sanitary container ready for your prescription.

ORTHO PHARMACEUTICAL CORPORATION (CANADA) LIMITED, TORONTO, ONT.

Henderson's

MATERIA MEDICA

NEW EDITION, completely revised and enlarged, by J. K. W. FERGUSON, and G. H. W. LUCAS, Department of Pharmacology, University of Toronto. $4.75.

Drugs from both the British Pharmacopoeia and the United States Pharmacopoeia are included in this volume, in such a manner that rapid comparisons may be made between British and American terminology. The text is also written on the basis that medical students will be taught to write prescriptions in English instead of Latin—a decision made by the Faculty of Medicine of the University of Toronto in 1947.

UNIVERSITY OF TORONTO PRESS

Trade Orders: S. J. R. Saunders

BABY TRUSTS the DOCTOR

and

THE DOCTORS FIND THEY CAN TRUST

"FARMER'S WIFE"

FOR EASY DIGESTION

Produced from the specially selected cows' milk of a Tuberculosis Accredited Free Area. Homogenized, irradiated and sterilized. Vitamin D potency of 400 International Units per reconverted quart.

Lower in Fat Content

Higher in Protein Value

Please write for literature and pocket formula card.

COW & GATE (CANADA) LIMITED

GANANOQUE, ONTARIO

INDIVIDUALIZED TREATMENT OF PERNICIOUS ANEMIA

AYERST LIVER EXTRACTS

Whether the patient suffers from an acute condition with neurological involvement or merely requires maintenance therapy to retain a normal blood picture, there is an Ayerst Liver Extract available for effective treatment.

INJECTABLE

No. 499 — Each cc. contains not less than 10 Units. In 1 cc. ampoules (boxes of 25 and 100) and in 10 cc. rubber-capped vials.

No. 530 — Each cc. contains not less than 15 Units. In 10 cc. rubber-capped vials.

INJECTABLE with THIAMIN CHLORIDE

No. 449 — Each cc. contains not less than 2 Units of crude liver together with 10 mg. of thiamin chloride. In 10 cc. rubber-capped vials.

LIQUID

No. 936 — Each tablespoonful represents the anti-pernicious anemia principle obtained from ¼ lb. fresh liver. In bottles of 10 oz.

CAPSULES

No. 350 — Each capsule contains the anti-pernicious anemia principle obtained from ⅓ oz. fresh liver. In bottles of 200 capsules.

CAPSULES with FOLIC ACID

No. 351 — Each capsule contains the anti-pernicious anemia principle obtained from ⅔ oz. fresh liver, with the addition of ½ mg. folic acid. In bottles of 100 capsules.

AYERST, McKENNA & HARRISON LIMITED

Biological and Pharmaceutical Chemists

MONTREAL CANADA

Can convalescence be hastened?

You have seen your patient successfully through a serious illness, accident, or surgery. The question now is "How can I shorten the period of convalescence?"

During the acute period the demand for vitamin B factors increases greatly and dietary intake is often limited. The reserve of these important factors is thus quickly lowered to a sub-optimum level.

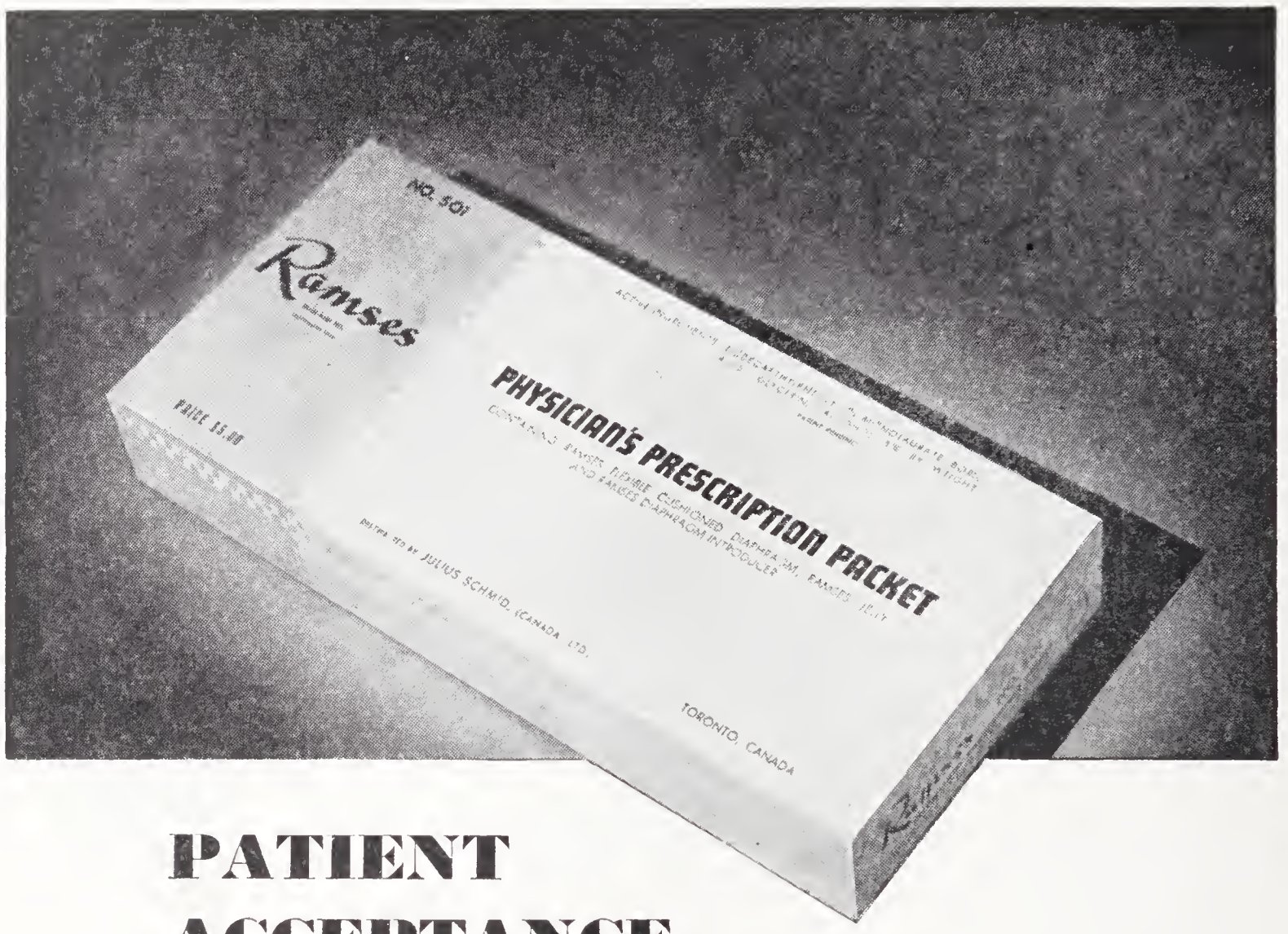
Most patients can be expected to convalesce more rapidly if given adequate amounts of a complete, well-balanced and potent preparation of the Vitamin B-Complex.

B·PLEX

Wyeth
Registered Trade Mark

admirably meets the need . . .

available in Elixir, Capsule and Injection form.



PATIENT ACCEPTANCE

Physicians can prescribe this complete unit with the confidence that it will prove acceptable to the patient while providing assured protection.

Evidence obtained from clinicians establishes that patients continue to use the technique embodied in the "RAMSES"* Prescription Packet No. 501 because of its effective and comfortable employment.

All "RAMSES" Gynecological Products are accepted by the Council on Pharmacy and Chemistry of the American Medical Association. They are available through recognized pharmacies.

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY AMERICAN MEDICAL ASSOCIATION

*The word "RAMSES" is a registered trademark.

JULIUS SCHMID (Canada) Ltd.

31 Teraulay St. • Toronto, Ont.

Edward Buckingham Shuttleworth

FOUNDED THIS FIRM

70

YEARS AGO

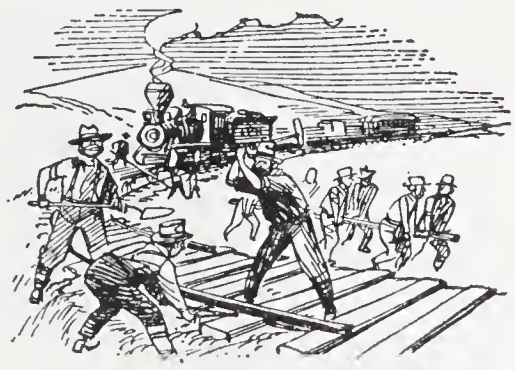
THE FATHER OF PHARMACY IN CANADA

Professor E. B. Shuttleworth is popularly known as the Father of Pharmacy in Canada. He was a prime mover in the establishment of suitable laws and standards in Pharmacy in Canada. He was the first Dean of the Ontario College of Pharmacy, Lecturer in Materia Medica at Trinity College and for many years edited the Canadian Pharmaceutical Journal. He founded The E. B. Shuttleworth Chemical Co. Ltd. in 1879 and for many years remained in active control of the company.

The E. B. Shuttleworth Chemical Company Limited has been serving the medical profession continuously since 1879.

The policies and principles laid down by its founder, Professor Shuttleworth, have been steadfastly upheld over the years. Although the company is so rich in tradition, with roots deeply set, it does not depend on this heritage for its success. It continues to delve into the scientific side of its business, originating and perfecting formulae and preparing pharmaceutical products which will measure up to the most exacting requirements of the medical profession.

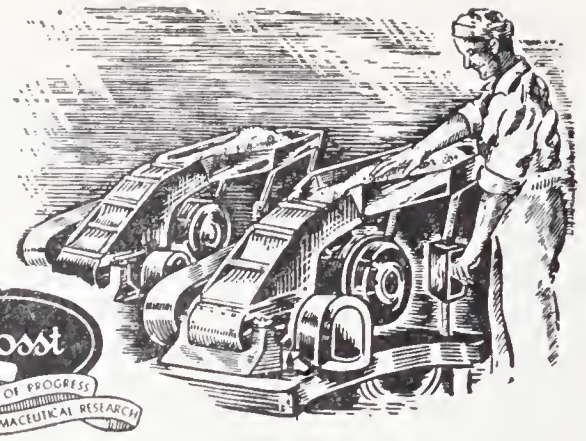
We are constantly investigating the new in the science of pharmacy, following every promising trend in the science of medicine and therapeutics. Our watchword for the years to come will always be "The Advancement of Pharmacy in Canada".



THE E. B. SHUTTLEWORTH CHEMICAL CO. LTD., TORONTO, CANADA

AN ALL CANADIAN COMPANY . . . SINCE 1879

THERAPEUTIC BRIEFS
from
Charles E. Frosst & Co.



RELIEF FOR THE UPSET STOMACH

"SEDALKA"

Granular Effervescent Salt "Frosst"

Upset stomach may be due to one, or a combination of a number of causes. Excluding organic diseases, which are associated with indigestion, one is left with a very large number of persons in whom an occasional "upset stomach" may be due to injudicious use of certain foods, taking food while under mental stress, hurrying meals without proper mastication, excessive smoking or excessive use of alcohol. In addition there is a large group of people, the "chronic belchers", who are usually tagged with a diagnosis of gastric neurosis.

Physicians are consulted many times about "upset stomach" and often after exhaustive investigation, come to the conclusion that there is no organic disease present and that the condition is probably due to one of the causes enumerated above. General instructions as to method and time of taking food, not eating while aggravated, etc., may all be very well, but are seldom carried out by the patient.

It will be found, more especially in patients with gastric neurosis, that a dose of "Sedalka" after each meal will neutralize excess gastric acid, mildly sedate the patient, and that the combination of these effects will tend to relieve patients suffering with gastric neurosis.

"Sedalka" too, has high potential systemic alkalinizing effect by virtue of its content of citrates. It will be found of value in raising the alkali reserve of patients, which may be diminished following overindulgence in alcohol and at the onset of acute infections.

"SEDALKA"

Granular Effervescent Salt "Frosst"

DOSAGE

Each heaping teaspoonful of half measuring-capful makes available:

Sodium phenobarbital	¼ gr.
Calcium carbonate	10 gr.
Sodium bicarbonate	5 gr.
Sodium citrate and Sodium tartrate (potential alkalis)	q.s.

We will be pleased to send clinical samples upon request

Charles E. Frosst & Co.
MONTREAL CANADA

OUR 50TH ANNIVERSARY YEAR

9-1